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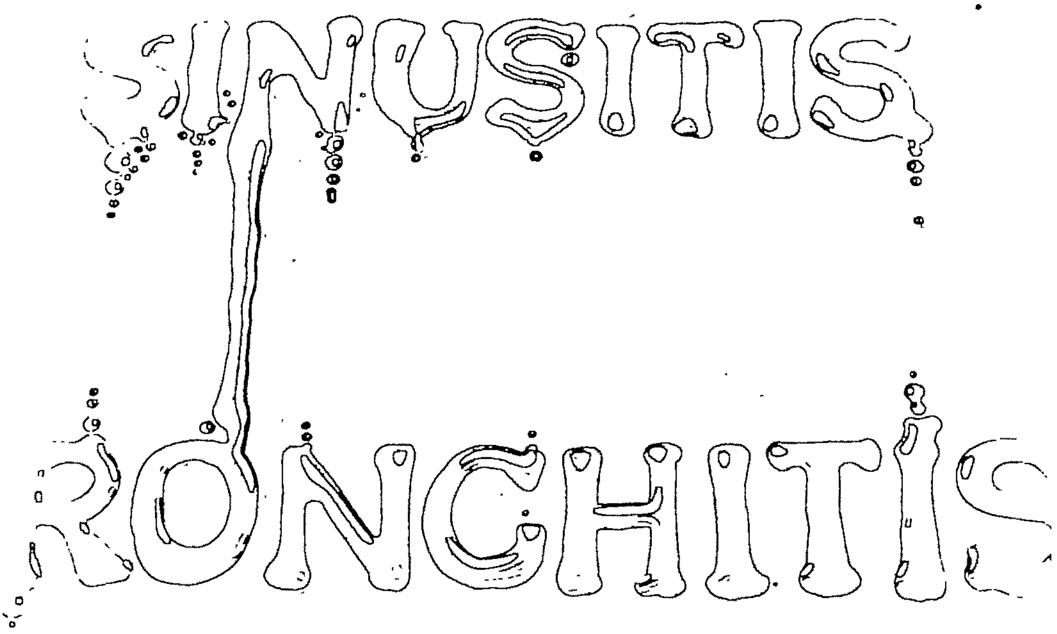

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EDITORIAL

Mr J. R. Belcher and Dr Leslie Capel retire from Editorship of the Journal with this issue. They have worked for many years to maintain the standards of the Journal and have earned the gratitude of readers, authors and publishers. The steady increase in both the contents and readership of the Journal over the past few years is a testimony to their work.

The policy of the Journal will remain unchanged under its new Editor with continuing emphasis on the needs and interests of practising clinicians.

Original articles are welcomed on any aspect of respiratory medicine, including surgery, physiology, pathology, epidemiology and radiology

Review articles on any topic relevant to respiratory medicine are usually commissioned by the Editor but authors may submit reviews for consideration and are encouraged to consult the Editor if they wish to write a review article for the Journal.

There will in addition be occasional series of linked reviews in consecutive issues.

Short communications will, if accepted, be published in the first possible issue of the Journal.

Articles are invited under the headings of '*Hypothesis*' or '*Controversy*', in which authors can present unproven hypotheses or discuss controversial issues in any field of respiratory medicine or research.

The Editor and the Editorial Board welcome suggestions, advice and critical comment to ensure that the Journal continues to fufil the needs of its readers.

J. E. Stark
Editor

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Review Article

PULMONARY OEDEMA

PHILLIP D. SNASHALL

Department of Medicine, Charing Cross Hospital, London

Pulmonary oedema is a condition in which there is an abnormal increase in the amount of extravascular lung water. Interstitial water is increased and at a later stage water enters the air spaces, flooding alveoli and causing airway foaming. Intracellular water may also be increased (Robin & Theodore 1976). This process represents a failure of the homeostatic mechanisms which regulate interstitial water; more water is filtered from capillaries and venules than can be removed by the lung lymphatics.

Reference above to 'abnormal' lung water presumes a knowledge of the normal lung water and its distribution between interstitium, air spaces and cells, as well as its physiological and regional variation. In fact this information is far from complete in experimental animals and there have been very few direct measurements in man (Gump et al. 1971). There is a physiological variation of normal lung water; the fetus has flooded air spaces and the neonate interstitial oedema (Humphreys et al. 1967), but otherwise the variability with age is unknown. Neither severe exercise (Vaughan et al. 1976) nor posture (Muir et al. 1972) have much effect on lung water. We do not know how lung water is affected by the menstrual cycle, pregnancy, weightlessness or sleep.

Pulmonary microvasculature

The bulk of the microvascular exchange surface area is in capillaries, but exchange may also take place across venules, arterioles and small arteries.

Pulmonary capillaries are the 'continuous' variety found in skin and skeletal muscle (Fig. 1). They consist of a single layer of endothelial cells with highly attenuated cytoplasm, joined at their edges by tight junctions. Prominent in their cytoplasm are vesicles which on electron micrographs may be seen as opening to the luminal or interstitial surfaces. The capillary is invested in a single, continuous layer of basement membrane. The capillary endothelium is the main barrier to movement of substances by bulk flow (filtration and reabsorption) or diffusion between capillary lumen and interstitium. Bulk flow (movement of a substance down a pressure gradient) is mainly restricted to the gaps between endothelial cells; diffusion (movement of a substance down its concentration gradient) also occurs through the endothelial pores, but small and lipid-soluble molecules can diffuse across the endothelial membranes and cytoplasm and thus equilibrate with the interstitium over an enormous surface area. These small molecules traverse water-filled pores 0.4–0.5 mm in radius.

Electron microscopic and physiological evidence suggest that the gaps at the endothelial junctions in skeletal muscle are of the order 3.5–5 nm in radius. In the lung, pores may be wider (Boyd et al. 1969; Blake & Staub 1972). They occupy only 1/10 000th of the surface area of the microvessel. The pore size is similar to the size of the albumin molecule which is therefore considerably impeded in its efflux from the capillary.

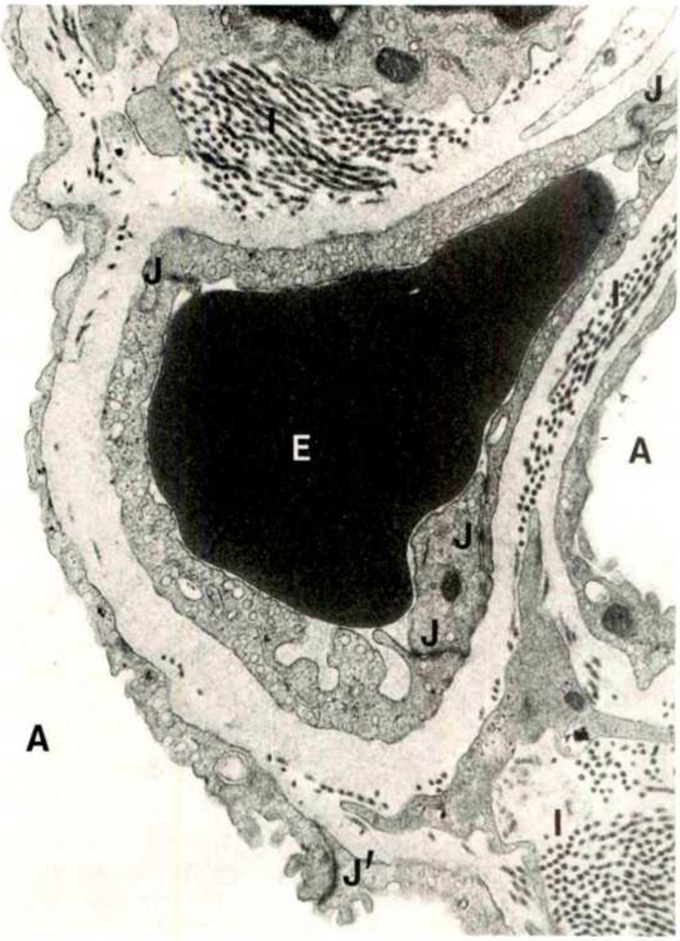

Fig. 1. Electronmicrograph of human alveolar septum showing a capillary filled with an erythrocyte (E) and, on either side, alveolar air spaces (A). The endothelium of the capillary wall contains numerous intracytoplasmic vesicles. Junctions (J) between endothelial cells consist of 'tight' and more open regions. Tight junctions (J′) are also seen between alveolar type I epithelial cells. Between the two cell layers, the interstitium largely consists of the opposed epithelial and endothelial basement membranes, but in some areas (I) the interstitium is wider and contains collagen fibrils. It can be seen that if oedema accumulates in these wider regions of the interstitium, there will be little effect on the alveolocapillary distance and little effect on gas exchange. × 32 200.

Despite their larger size, globulins and fibrinogen also traverse the microvascular membrane and find their way into lung lymph (Boyd et al. 1969). The role of endothelial vesicles in the transport of these larger molecules is disputed. Perhaps the largest molecules travel via a very small population of 'large pores' or vesicles (Bruns & Palade 1968).

Bulk flow through the microvascular membrane depends upon the microvascular and perimicrovascular hydrostatic and colloid osmotic pressures, and membrane permeability, according to the Starling relationship (Fig. 2):

$$\dot{Q}_f = K_f \, [(P_{mv} - P_{pmv}) - \sigma(\pi_{mv} - \pi_{pmv})]$$

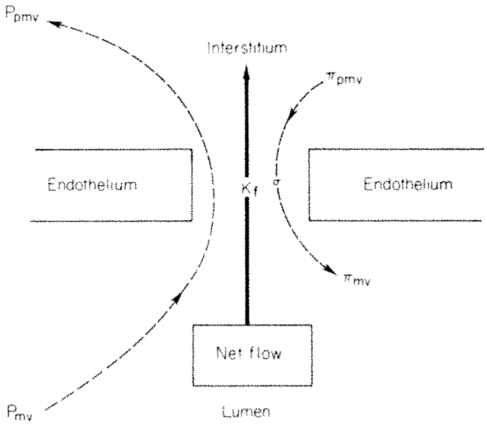

Fig. 2. Pressures and flow across the endothelium. Pressures (- - - →) acting across the microvascular endothelium cause flow (→) through junctions between endothelial cells. The transvascular hydrostatic pressure difference, $P_{mv}-P_{pmv}$ (microvascular pressure − perimicrovascular pressure), tends to filter water out of the vessel but this is countered by a protein osmotic force in the opposite direction. The latter is due to the difference of plasma protein osmotic pressure between the vessel (π_{mv}) and interstitium (π_{pmv}) acting at the junction. The full osmotic pressure, however, is not developed since the endothelium is a 'leaky' semipermeable membrane. This property of the junction is characterized by σ, the reflection coefficient for plasma proteins. For the perfect semipermeable membrane $\sigma=1$, but for a 'leaky' membrane σ is between 0 and 1; in the lung the value is approximately 0.8. The balance of forces causes net filtration out of the microvessel. The volume of filtrate for a given imbalance of pressures depends on the conductivity, K_f, of the junctions

where $\dot{Q}_f$ is net transvascular water flow, K_f is the filtration coefficient, P_{mv} and P_{pmv} are microvascular and perimicrovascular hydrostatic pressures, π_{mv} and π_{pmv} are microvascular and perimicrovascular colloid osmotic pressure and σ the membrane reflection coefficient for plasma proteins (which allows for the fact that the microvascular membrane is a slightly leaky semipermeable membrane). When lung water is not changing $\dot{Q}_f$ must be equal to $\dot{Q}_l$, the lung lymph flow. The Starling relationship is demonstrably true in a general sense: lung lymph flow may be increased by raising pulmonary microvascular pressure (Erdmann et al. 1975) (Fig. 3) or permeability (i.e. increasing K_f and decreasing σ) (Brigham et al. 1974). However, precise quantitative validation is at present impossible. With the sole exception of plasma colloid osmotic pressure, there is doubt and disagreement about the magnitude of all the variables in the Starling relationship. In addition, in a lung with any vertical height, regional microvascular filtration will vary with height owing to the effect of gravity on microvascular pressure and possibility on tissue hydrostatic and osmotic pressures (Staub 1974).

Microvascular pressure

Lung microvascular pressure has never been measured and there is consequently doubt and disagreement on the relationship of microvascular pressure to arterial and left atrial pressures (Gaar et al. 1967; Glazier et al. 1969; Fung & Sobin 1969). The balance of evidence favours an approximate equality between arterial and venous vascular

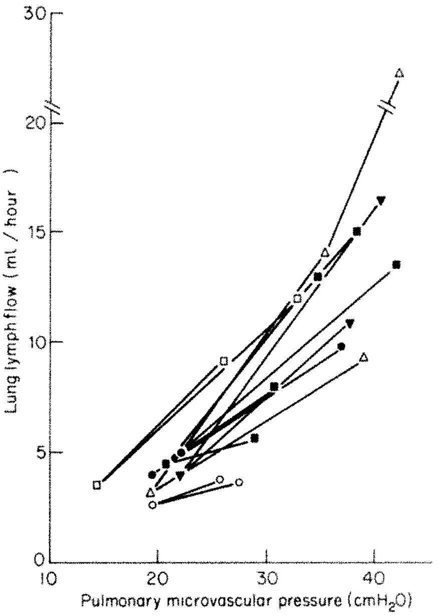

Fig. 3. Effect of increasing pulmonary microvascular pressure on lung lymph flow in the sheep. Different symbols indicate different sheep. Lymph flow consistently increases when microvascular pressure is raised. (*Reproduced from Erdmann et al. 1975*)

resistances and hence microvascular pressure should lie midway between arterial and left atrial pressure (Gaar et al. 1967). However, not all of the lung lies at the level of the pulmonary artery or left atrium. In upright man the lung base is approximately 15 cm below and the apex 15 cm above these structures and consequently there will be a hydrostatic gradient of pressure from top to bottom of approximately 30 cmH$_2$O, with the apical pressure being close to zero (West 1965). Approximately 80% of the lung mass is below the hilum (Staub 1974).

Pulmonary interstitial space

Compared with the body as a whole, the lung has a large interstitial space, containing approximately half the extravascular lung water and comprising approximately a third of blood free lung weight (Snashall et al. 1976). It is the compartment primarily involved in the oedema process. The lung interstitium is divided into that in the lung parenchyma (mainly the alveolar septae) and the extra-alveolar interstitium which surrounds blood vessels and bronchi, forming a pathway from parenchyma to hilum.

The alveolar interstitium is an exceedingly attenuated structure sandwiched between the vascular endothelium and alveolar epithelium. The total thickness of the sandwich is less than 1 μm and the interstitium is mainly composed of endothelial and epithelial basement membranes, and bundles of collagen fibres, although there are areas of looser tissue in which oedema may develop (see Fig. 1). Lymphatics have not been demonstrated in the alveolar interstitium, but unmyelinated nerve fibres (perhaps J fibres?) have been seen in the rat lung (Meyrick & Reid 1971). In mild oedema the parenchyma seems to be spared, with the fluid preferentially accumulating in the extra-alveolar interstitium (Staub et al. 1967). This latter compartment has a loose, distensible structure and contains lymph vessels and capillaries. The accumulation of oedema produces 'cuffs' around blood vessels and in severe oedema these may extend around airways (Muir et al. 1972) (Fig. 4). It has been suggested (West et al. 1965) that cuffs, particularly at the lung bases, may compress blood vessels causing a redistribution of blood flow to the lung apex, as, for instance, occurs in mitral stenosis (Dollery & West 1960). This suggestion has been refuted (Ritchie et al. 1969) and, in fact, the redistribution of flow that occurs in oedema *per se* is far less than is seen in mitral stenosis (Muir et al. 1972). There is, however, evidence that cuffs may compete for space in the extra-alveolar compartment with peripheral airways causing an increase of peripheral airway resistance (Hogg et al. 1972) and closing volume (Muir et al. 1975).

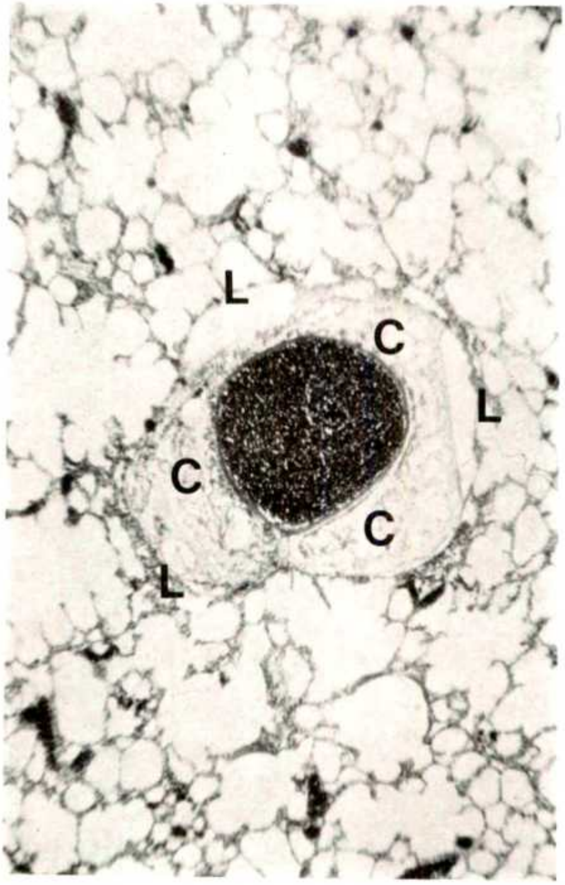

Fig. 4. Photomicrograph of oedematous dog lung showing a small pulmonary vein surrounded by a cuff (C) of oedema. Dilated lymphatics (L) are seen at the periphery of the cuff. × 70

Interstitial hydrostatic pressure

This cannot be measured directly. Indirect measurements in isolated lung lobes (Nakahara et al. 1976) suggest that interstitial pressure in the alveolar septum is close to or slightly above alveolar pressure. There is no convincing evidence for the widely quoted belief that alveolar interstitial pressure is markedly subatmospheric (Guyton 1969). On the other hand, extra-alveolar interstitial pressure is probably subatmospheric and probably lower than pleural pressure due to the phenomenon of interdependence (Howell et al. 1961).

Thus liquid filtered from a microvessel in the alveolar septum will drain a distance of approximately 1 mm down a pressure gradient into the extra-alveolar interstitium where it may enter a lymph capillary or accumulate as a cuff of oedema. Extra-alveolar interstitial pressure will therefore rise and will eventually equal alveolar interstitial pressure, when oedema may begin to accumulate in the septum. When extra-alveolar interstitial pressure equals airway pressure, liquid might be expected to cross from the cuffs into airways since the airway wall and epithelium is freely permeable to water and plasma protein (Staub et al. 1976). This may be a pathway by which alveolar flooding occurs in severe oedema.

It is therefore frequently suggested (Hurley 1978) that the interstitium protects the alveoli from flooding by providing a 'sink' in which oedema preferentially accumulates. Indeed, standard histological preparations show well developed interstitial oedema without evidence of oedema in airspaces (Staub et al. 1967). However, oedema proteins tend to be washed from air spaces during fixing and staining (Visscher et al. 1956) and it is likely that the amount of air space oedema is underestimated. We have recently examined unfixed frozen sections of oedematous lung (Snashall et al. 1978). When viewed by reflected light, ice crystals are usually seen in both air spaces and interstitium, even in lung regions with minimally ($<20\%$) increased extravascular lung water. It was relatively uncommon to see pure interstitial oedema. We therefore question whether the accepted sequence of liquid accumulation in oedema is as clear-cut as has been suggested.

Interstitial protein osmotic pressure

Most data on the composition of lung interstitial liquid come from the composition of lung lymph, which is probably identical to interstitial liquid (Nicolaysen et al. 1975; Vreim et al. 1976*a*, *b*). In a resting conscious sheep the protein osmotic pressure of pure lung lymph averages 60–70% of the simultaneous plasma protein osmotic pressure (Brigham et al. 1974) and thus the osmotic pressure generated across the microvascular membrane is much less than is commonly assumed. If, however, microvascular pressure is raised, water flux into the interstitium increases while protein flux hardly changes and hence interstitial protein concentration and osmotic pressure fall. The osmotic gradient across the microvascular membrane therefore increases and diminishes further filtration. This represents an important homeostatic mechanism to prevent lung oedema from increases of microvascular pressure. Erdmann et al. (1975) calculated that for a 10 cmH_2O increase in pulmonary microvascular pressure, the protein osmotic gradient would increase by 5 cmH_2O, thus 'buffering' 50% of the increase in filtration pressure (Fig. 5).

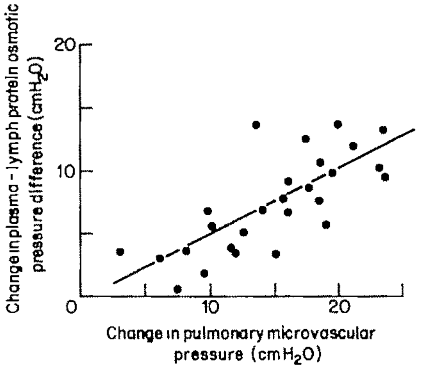

Fig. 5. Effect of increasing microvascular pressure on the plasma–lymph protein osmotic pressure difference in sheep. As microvascular pressure increases the lymph protein concentration falls and the difference between osmotic pressures of plasma and lymph increases. This increased osmotic pressure difference tends to limit the increase in microvascular filtration due to the increased hydrostatic pressure. The straight line of best fit has a slope of 0.5 indicating that for a rise in microvascular pressure of 10 cmH_2O the osmotic gradient will increase by 5 cmH_2O. (*Reproduced from Erdmann et al. 1975*)

Lung lymphatics

Lauweryns and Baert (1977) have summarized current knowledge of lung lymphatic anatomy and physiology. The function of lymphatics is to remove protein and water from the interstitium. Protein can diffuse across the vascular endothelium and in the absence of lymph drainage interstitial and plasma protein concentrations would equalize.

Lymph flow increases promptly on increasing microvascular pressure (Erdmann et al. 1975) or permeability (Brigham et al. 1974) because of an increase in filtration. Lymph protein concentration reflects that of the filtrate, being low when microvascular pressure is raised and high when microvascular permeability is increased. With chronic elevations of microvascular pressure (as for instance in mitral stenosis) there is evidence that the lung lymphatics in some way increase their capacity to carry lymph. Thus, in dogs with chronic heart failure and pulmonary oedema due to aortacaval anastomosis, lymph flow rates were many times greater than those produced acutely by elevation of pulmonary microvascular pressures (Uhley et al. 1962), although it was never adequately demonstrated that all the increased lymph flow originated from the lungs. The dogs had gross peripheral oedema.

Alveolar epithelial membranes

The alveolar type I cells, forming a continuous epithelial sheet, constitute the major barrier preventing the movement of interstitial liquid into the air spaces. Anatomical (Schneeberger & Karnovsky 1976) and physiological (Taylor & Gaar 1970) studies demonstrate that the junctions between type I cells are 'tight' with pores of radius 0.6–1.0 mm.

The epithelium lining the airways is more permeable than that lining alveoli, offering little restriction to the diffusion of protein (Staub et al. 1976). It is interesting that in pulmonary oedema produced either haemodynamically or by an increase in vascular permeability, alveolar liquid and interstitial liquid have similar protein composition (Vreim et al. 1976*a*, *b*) although, at least in the case of haemodynamically produced oedema, the alveolar epithelium is intact and presumably impermeable to protein. It is possible that liquid crosses the more permeable airway wall from peribronchial cuffs and thus drains into alveoli.

DIAGNOSIS OF PULMONARY OEDEMA

Massive pulmonary oedema is easily diagnosed. It is associated with characteristic symptoms and signs with radiographic and blood gas changes. The problem is to detect smaller abnormal accumulations of lung water at a stage before lung function is compromised and the patient is discomforted by shortness of breath. It is commonly assumed that current methods of oedema detection are crude: Fishman (1976) has suggested that lung extravascular water must be increased by 600% before it becomes clinically detectable! Improvement in lung function may follow administration of diuretics without there being radiological pulmonary oedema (Noble et al. 1966), but others have emphasized the usefulness and sensitivity of the radiograph in diagnosis before symptoms or signs of pulmonary oedema are present (Harrison et al. 1971; Chait et al. 1972).

Chest radiograph

Both interstitial and alveolar oedema may cause radiographic changes. In haemodynamic pulmonary oedema there will usually, in addition, be signs of pulmonary venous hypertension with engorgement of upper zone veins (McHugh et al. 1972) in films taken in the upright posture. This may be explained as follows: at normal pulmonary vascular pressures in the upright posture blood flow is highest in the lower lung zone and least at the apex; raising vascular pressures produces a more even distribution of perfusion (West et al. 1964) and increased filling of upper zone vessels. The upper zone veins will also act as a manometer in the left atrium and will fill as left atrial pressure rises. When pulmonary venous pressure is chronically elevated, as in mitral stenosis, there may be secondary reflex vasoconstriction in the lower zone pulmonary arteries producing a true inversion of the normal distribution of blood flow, with more going to the lung apex than base (Dollery & West 1960). Pulmonary oedema itself, when severe, may also cause some redistribution of flow away from the flooded lung bases (Muir et al. 1972) but left ventricular failure is not usually associated with an inversion of the normal flow distribution.

Cuffs of interstitial oedema may cause an increase in size of the hilar shadows and vascular markings; peribronchial cuffs may show when airways are viewed end-on, particularly in the lateral radiograph (Gleason & Steiner 1966). Kerley A, B and C lines (Kerley 1933; Slavin et al. 1975) are caused by interstitial oedema in fibrous septae. The B lines are the most important and are seen laterally at the lung bases and caused by oedema in the fibrous septae between secondary lobules with a minor contribution from dilated lymphatics also lying in this plane (Fleischner & Reiner 1954).

Air space flooding produces a diffuse or 'acinar' shadowing in the lung fields that typically extends from the hilum, where the vascular marking becomes blurred, to involve the peripheral lung fields of the lower zones more than the upper. The margins of the process are poorly defined and an air-bronchogram may be seen. The process may be patchy, as for instance in high-altitude pulmonary oedema in which the lung bases are characteristically spared. Alveolar oedema may produce a 'butterfly' (Nessa & Rigler 1941) or 'bat's-wing' (Hodson 1950) pattern in which central shadowing is sharply demarcated from clear peripheries. This distribution, originally described in azotaemia, is also seen in congestive heart failure, neurogenic pulmonary oedema, polyarteritis nodosa and collagen disorders (Herrnheiser & Hinson 1954). There is no satisfactory explanation for the sharp demarcation of the oedema, although various hypotheses have been suggested (Fleischner 1967).

The sensitivity of the chest radiograph to the presence of abnormal lung water in left-heart failure has been determined in man by measurement of pulmonary extravascular water by the double indicator dilution method (Yu 1971; Fazio et al. 1976). These studies suggest that the radiograph becomes abnormal when lung water increases by 30–80%. The double indicator dilution method, however, may overestimate lung water in left-heart failure (see below). We have recently attempted to relate radiographic changes to gravimetrically measured extravascular lung water in the dog (Snashall et al. 1978). A diffuse increase in hazy shadowing was reliably recognized by a chest radiologist when lung water was increased by more than 30% above the mean normal value, whether or not a control film was available for comparison. Without the control film, however, the radiologist tended to diagnose oedema when lung water was normal. The main importance of having a control film for comparison is in the recognition of normality.

All animals that developed pulmonary oedema showed a decrease in their radiographic lower zone lung volume associated with an elevation of the diaphragm. The loss of volume showed little correlation with extravascular lung water and large changes in volume were seen in dogs with lung water increased as little as 20%. Elevation of the diaphragms is commonly seen clinically, although it is usually discounted as being due to the patient's inability, when sick and breathless, to make an adequate inspiratory effort. Most radiological texts fail to discuss volume changes in oedema even though their illustrations frequently show prominent changes in diaphragm level occurring as oedema develops or clears. Kreel and Sandin (1977) have pointed out that diaphragm position may be a valuable radiographic sign of lung oedema.

Râles, crepitations and crackles

Crackles is the best English term for the non-musical explosive sounds heard over the chest in pulmonary oedema and other conditions (Robertson 1963). It is thought that these sounds are produced when bronchioles snap open during inspiration (Forgacs 1967). They occur in association with oedema, possibly because the lung bases are at a low volume and airways are therefore not held open throughout the respiratory cycle.

In 94 patients suffering from acute myocardial infarction, Chait et al. (1972) found 31 with radiological evidence of oedema, but no lung crackles, gallop rhythm or breathlessness, suggesting that a critically viewed radiograph is more sensitive than clinical signs. Of 45 patients with clinically diagnosed oedema 43 had radiographic changes.

Other techniques for detection of pulmonary oedema

Dissatisfaction with clinical methods and the radiograph has led to the development of a variety of techniques, none of which has been accepted for routine clinical use. Indicator dilution methods have been extensively used and involve measuring the difference in mean transit time through the pulmonary circulation of two simultaneously injected indicators: one non-diffusible substance that remains intravascular and one diffusible substance that equilibrates with lung extravascular water within the transit time. The method usually involves the collection of arterial blood, but an external counting adaptation has been described (Fazio et al. 1976). Unfortunately in experimental animals the lung extravascular water volume measurable with this technique is on average only two-thirds of the actual lung water measurable by drying (Staub 1974), and this fraction seems to depend on the evenness of perfusion. Thus the apparent lung water increases with exercise in association with a similar increase in perfused gas volume (Crosbie et al. 1971; Marshall et al. 1971) but does not when pulmonary oedema is caused by microvascular damage (Pearce et al. 1965) owing to inhomogeneity of perfusion and diversion of perfusion away from oedematous areas (Muir et al. 1972). This seems a crushing disadvantage in a method for clinical use. There are suggestions that the method is more sensitive than the radiograph in detecting haemodynamically produced oedema (Fazio et al. 1976).

The measurement of lung density can be made using the Compton scatter principle (Garnett et al. 1977) or by computerized axial tomography. Density is markedly influenced by lung inflation, but may prove a useful index. The uptake of inhaled highly soluble gases such as acetylene or ether has also been used to measure the pulmonary tissue mass (Louderbough et al. 1976), but abnormal lung water will not be detected if it is in unventilated lung. The transmission and reflection of microwaves (Bragg et al. 1977) is also affected by lung water and their use is being assessed.

Lung function testing may suggest that pulmonary oedema is present, although no quantitation is possible. Thus, Van Leeuwen et al. (1973) showed that vital capacity falls with pulmonary oedema and pulmonary vascular congestion in patients with left ventricular failure. Muir et al. (1975) showed that closing volume increased during rapid intravenous volume loading in normal man, although it was not demonstrated that this effect was due to pulmonary oedema. Hogg et al. (1972) found that with both pulmonary vascular congestion and pulmonary oedema the air flow resistance of bronchioles increased markedly while the resistance of central airways was little altered.

CAUSES OF PULMONARY OEDEMA

Pulmonary oedema is due either to an increased microvascular pressure (with or without aggravating factors such as a low plasma colloid osmotic pressure or lymphatic obstruction) or to increased microvascular permeability, or to a combination of both.

Increased microvascular pressure

This may be ***cardiac*** due to left ventricular failure or mitral valve obstruction or ***non-cardiac*** as in extracellular fluid volume overload or pulmonary veno-occlusive disease.

Several groups have shown that pulmonary microvascular pressure must be raised above a certain threshhold value of 20–30 cmH_2O before any detectable increase in lung water occurs. This is testimony to the effectiveness of homeostatic mechanisms (increased lymph flow, decreased interstitial colloid osmotic pressure) that protect the lung against fluctuations of microvascular pressure. A decrease in plasma colloid osmotic pressure lowers the threshhold value (Guyton & Lindsey 1959).

Pulmonary vascular pressures can vary more rapidly than lung water and hence pulmonary artery, left atrial or wedge pressures may have returned to normal when the lungs are still oedematous (Nixon 1968) and this may create the impression that oedema has developed with normal vascular pressures.

Obstruction to pulmonary lymphatics can occur due to silicosis, lymphangitis carcinomatosa and lung transplantation and there is evidence that in the presence of such obstruction the lung is particularly susceptible to oedema when microvascular pressure is elevated (Cross et al. 1970).

Pulmonary oedema with increased microvascular permeability

An increased microvascular permeability may cause a breakdown in the homeostatic mechanisms controlling bulk flow across the endothelium; if water permeability is increased then any increase of microvascular pressure will cause rapid filtration that is unopposed by protein osmotic pressure which has been diminished by (*a*) the endothelium now being a less effective semipermeable membrane or (*b*) an increased interstitial protein concentration. Under these circumstances oedema may form with great rapidity.

Generally the change in permeability is assumed from the development of oedema with normal vascular pressures, though occasionally expectorated oedema fluid has been collected and shown to be rich in protein ($>70\%$ of plasma concentration when permeability is increased) (Robin et al. 1972). If oedema is due to increased pressure, oedema fluid protein is low ($<50\%$) (Vreim et al. 1976*a*, *b*).

Damage to the microvascular membrane may be *acute*, due to inhalation of noxious gas such as phosgene, ozone, oxides or nitrogen (silo-filler's disease), smoke (Gelb & Klein 1976), or due to a circulating toxin such as heroin (Duberstein & Kaufman 1971), hydrocarbons (Cane et al. 1977), alloxan (Staub et al. 1967; Goetzman & Visscher 1969), alpha-naphthythiourea (Visscher et al. 1956), coral snake venom (Ramsey et al. 1971), autologous blood (Ward et al. 1968), dextran 40 (Kaplan & Sabin 1975), scorpion stings (Gaitonde et al. 1978) or organophosphate insecticides (Wadia & Sadagopan 1973). Alternatively it may be part of a *subacute* lung inflammation such as occurs after Paraquat poisoning, Gram-negative septicaemia (Harrison et al. 1969), oxygen poisoning (Bean & Zee 1966) and the 'adult respiratory distress syndrome' (Blaisdell & Stallone 1970). There may be a *chronic* increase in permeability in uraemia (Crosbie et al. 1972) or in immunological conditions such as Goodpasture's syndrome. Other than heroin, drugs such as nitrofurantoin, busulphan and hexamethonium may also produce oedema (Robin et al. 1973). The ultrastructural findings associated with increased microvascular permeability have been recently reviewed by Hurley (1978).

Pulmonary oedema of unknown mechanism—high-altitude pulmonary oedema

This typically occurs in children and young adults who rapidly ascend to over 2200 m and immediately indulge in heavy exercise such as climbing or skiing. It also occurs in high-altitude residents who return from a period at lower elevation (Scoggin et al. 1977).

The oedema has a patchy distribution that usually spares the bases and the condition resolves rapidly on return to a lower altitude or the administration of oxygen. The mechanisms are unknown. Hypoxaemia alone does not damage the endothelial membrane (Goodale et al. 1970). Subjects who have recovered from an attack have an abnormally brisk increase in pulmonary artery pressure with hypoxaemia and exercise (Hultgren et al. 1971). Pulmonary artery pressure is high during an attack, but wedge pressure is normal (Hultgren et al. 1964). Of course, pulmonary hypertension is not usually associated with pulmonary oedema unless venous pressure also is elevated, but in high altitude oedema it may be that due to hypoxaemic vasoconstriction, the whole (high) cardiac output is directed through a very restricted vascular bed with consequent microvascular hypertension and patchy oedema. The oedema will cause further hypoxaemia and further vasoconstriction. The dramatic effect of oxygen may be explained by the relief of hypoxaemic vasoconstriction and the diversion of perfusion to previously unperfused and unoedematous lung. Of course, such a hypothesis does not exclude the possibility that hormones, vasoactive amines or intravascular coagulation may be involved (Singh et al. 1969).

Pulmonary embolism

Pulmonary oedema is a frequent but poorly recognized complication of severe pulmonary embolism (White 1940; Yuceoglu et al. 1971) which occurs particularly when embolism is associated with pre-existing heart disease (Short 1952). Most standard textbooks fail to mention this complication, which is present in 50% of patients who die of pulmonary embolism (Yuceoglu et al. 1971). The presence of oedema may, in part, explain the hypoxaemia characteristic of pulmonary embolism. Although pulmonary arterial pressure rises after embolism, left atrial pressure and wedge pressure do not change significantly (Singer et al. 1957; Parmley et al. 1962). Pulmonary microvascular permeability may increase (Staub et al. 1977). The pressure and permeability changes may be mediated by vasoactive substances such as histamine (Laurent et al. 1957) or serotonin and other agents released by aggregating platelets (Gurewich et al. 1968). The diversion of the whole cardiac output through a small proportion of the vascular bed may result in oedema in the same way as has been suggested in high-altitude oedema (Hultgren et al. 1966).

Neurogenic pulmonary oedema

Pulmonary oedema may complicate head injuries, cerebrovascular accidents and epileptic convulsions (Chang & Smith 1967). In animals, oedema develops very rapidly after CNS injury and its development is preceded by a sharp and severe rise of pulmonary arterial and venous pressures (Luisada 1967) which then subsides as oedema continues to develop (Harari et al. 1976). The oedema may be prevented by pre-treatment with sympatholytic agents (Mackay 1950; Bean & Beckman 1969), and anaesthetic agents (Bean & Beckman 1969). The persistence and continued development of oedema after pulmonary vascular pressures have returned to normal suggests that the pulmonary microvasculature has been injured, possibly by the high pressure. This suggestion is supported by the high protein content of the oedema fluid, which approaches that of plasma (Cameron & De 1949).

Oedema due to re-expansion of a lung

Sudden pulmonary oedema is sometimes seen when a lung, collapsed by pneumothorax or effusion, is reinflated (Fig. 6). Pavlin and Cheney (1975) demonstrated in rabbits that collapse must be sustained for several days and also showed that the lung before expansion had normal water content. The usual explanation (Robin et al. 1973) is that interstitial pressure is abnormally low in the re-expanded lung and that this extravascular force draws liquid into the interstitium. However, this can be only a partial explanation since the oedema is often massive with apparent alveolar flooding.

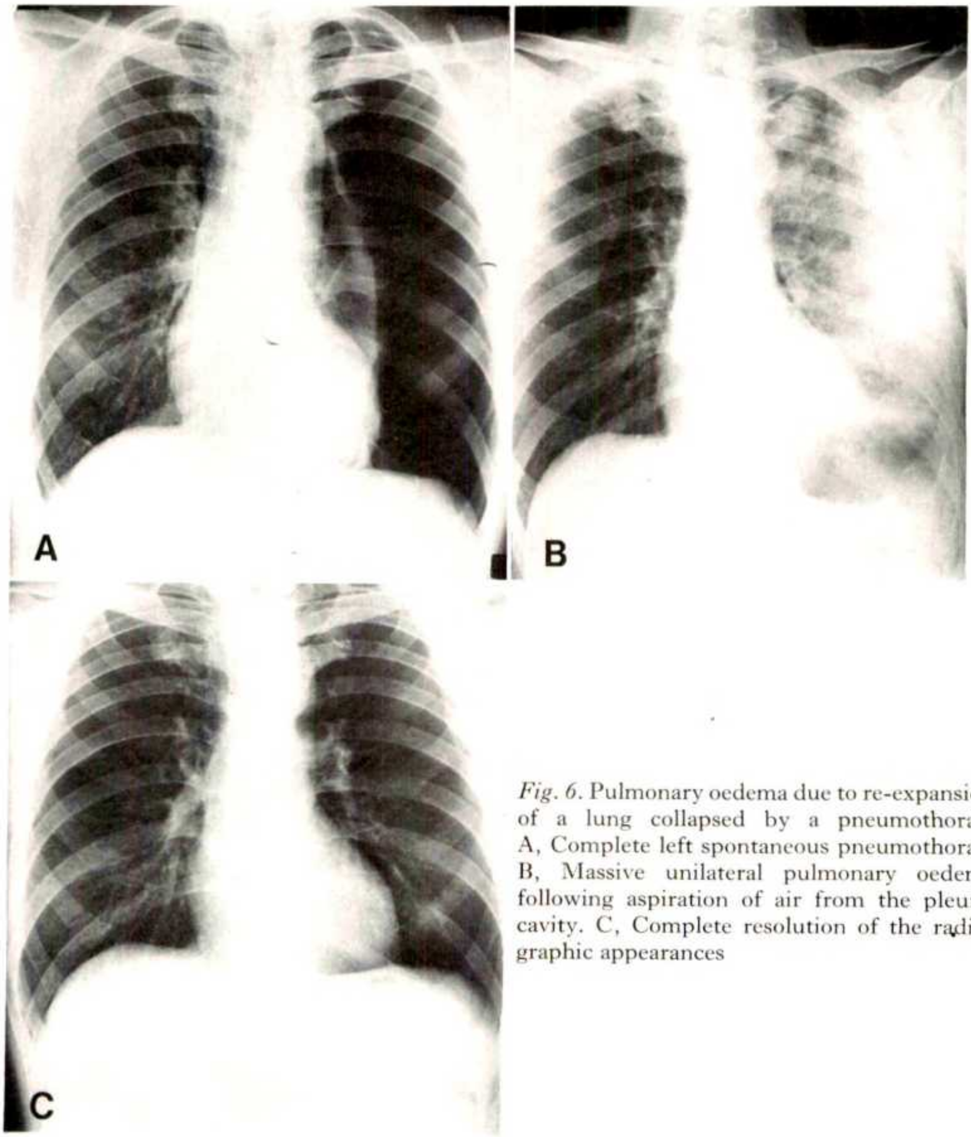

Fig. 6. Pulmonary oedema due to re-expansion of a lung collapsed by a pneumothorax. A, Complete left spontaneous pneumothorax. B, Massive unilateral pulmonary oedema following aspiration of air from the pleural cavity. C, Complete resolution of the radiographic appearances

TREATMENT OF PULMONARY OEDEMA

This is treatment of the underlying condition such as volume overload, cardiac failure or heroin intoxication plus supportive treatment dictated by the physiological consequences of lung oedema such as hypoxaemia, acidaemia and dyspnoea.

Hypoxaemia

The degree of hypoxaemia is variable, but often profound (Diamond et al. 1976). It is largely due to the persistence of perfusion to unventilated flooded alveoli resulting in a 'parenchymal shunt'. Alveolar ventilation is usually increased inasmuch as this can be demonstrated by a low arterial blood $P\text{CO}_2$. High concentrations of inspired oxygen are usually required to correct the hypoxaemia. Unfortunately it is not uncommon to see desperately hypoxaemic, overbreathing patients being given oxygen through 'controlled' oxygen masks such as the Ventimask or Edinburgh mask in the mistaken belief that high concentrations of oxygen are dangerous. It is possible that patients have died because of this. An inspired concentration of 75% may be obtained with 8 litres/minute through an MC mask, polymask or pneumask (Cotes 1975). If, on this treatment, inspired concentration arterial $P\text{O}_2$ does not rise above 50 mmHg (6.65 kPa) positive-pressure ventilation may be indicated. The rationale for positive-pressure breathing is that flooded and collapsed alveolar units are reinflated and again take part in gas exchange despite their abnormal water content (Said et al. 1964). There is no scientific basis for the popular myth that raising alveolar pressure 'pushes oedema back into the circulation'. Gravimetrically measured extravascular lung water is not significantly changed by continuous positive-pressure breathing (Demling et al. 1975) but clearly the effect on gas exchange of alveolar oedema is lessened by improving inflation. It seems that continuous rather than intermittent positive-pressure ventilation produces the greater benefit to gas exchange, presumably by preventing alveolar collapse during expiration. However, positive-pressure breathing, particularly continuous positive-pressure, reduces venous return and therefore cardiac output. There is always a danger of tension pneumothorax and surgical emphysema.

Hypercapnia and acidaemia

Although pulmonary oedema is usually associated with a normal or low arterial blood $P\text{CO}_2$, a significant minority of patients have CO_2 retention; this can be extreme and may be present before the administration of morphine. Bronchial obstruction from airway foam and bronchoconstriction would seem a likely explanation for this. In cardiogenic pulmonary oedema there may also be a metabolic acidosis, secondary, one assumes, to poor peripheral and hepatic perfusion and associated with increased lactate and pyruvate levels (Agostoni 1967). Avery et al. (1970) estimated that approximately 25% of patients presenting with cardiogenic pulmonary oedema have a combined respiratory and metabolic acidaemia with isolated respiratory or metabolic acidosis in another 10%. In Diamond's series, only 17% of patients with cardiogenic pulmonary oedema were acidaemic and approximately 40% of these had respiratory acidosis, 20% metabolic acidosis and 40% combined respiratory and metabolic acidosis (Diamond et al. 1976). Their acidaemic patients tended to be more hypoxaemic than non-acidaemic patients.

The awareness of this hypercapnic, acidaemic group of patients should prompt the measurement of arterial blood gases in all patients presenting with pulmonary oedema. This group cannot be recognized clinically (Aberman & Fulop 1972).

One is confronted with therapeutic dilemmas in trying to treat these acidaemic patients. Since acidaemia impairs cardiac function (Neaverson 1966), one is anxious to correct the abnormality with bicarbonate, but, in so doing, one is administering a considerable sodium load which will aggravate the oedema. A further danger of changing the blood pH with bicarbonate is the Bohr shift that this produces in the oxyhaemoglobin dissociation curve. In acidaemia the curve is shifted to the right with a decrease in affinity for oxygen and consequent easier unloading in the tissues. Bicarbonate will shift the curve to the left and may lead to tissue hypoxia. Agostoni (1967) and Avery et al. (1970) advised prompt correction of acidosis while Aberman and Fulop (1972) did not routinely use bicarbonate and found that the acid–base disturbance rapidly corrected when the oedema was treated. Likewise Diamond et al. (1976) did not use bicarbonate and had no fatalities in 82 patients.

Similarly, one is in a dilemma over the use of morphine in patients with hypercapnia. Although a cautious attitude is indicated, the evidence suggests that morphine does not usually cause significant respiratory depression in patients with pulmonary oedema, even when there is CO_2 retention (Aberman & Fulop 1972; Diamond et al. 1976). Blood gas monitoring is, however, essential.

Diuretics

Along with oxygen, the powerful diuretics frusemide and bumetanide administered intravenously constitute the mainstay of emergency treatment for pulmonary oedema. These agents have few important side effects unrelated to their diuretic action and have a very wide therapeutic range. They should be used in the dose necessary to produce an adequate diuresis while being aware of the possibility of hypovolaemia and even shock resulting from excessive diuresis. Several authors (Biagi & Bapat 1967; Bhatia et al. 1969) have commented that improvement seems to occur before the diuresis begins. This improvement may be due to an action on the peripheral circulation causing vasodilatation and an increase in venous capacitance with a decrease in left ventricular filling pressure and increase in renal blood flow (Dikshit et al. 1973). The therapeutic importance of these peripheral vascular changes has not been defined.

Venous congesting cuffs and bleeding

Since the advent of powerful, rapidly acting diuretics these direct methods of decreasing central venous pressures have been less frequently employed. Bleeding is effective but may be dangerous. Venous congesting cuffs on the limbs are probably ineffective. Habak et al. (1974) found that there was no significant fall in pulmonary wedge pressure when cuffs around both thighs and one arm were inflated (to 20, 40 or 60 mmHg) in patients with left ventricular failure. They demonstrated that the veins were relatively undistensible in heart failure when compared with those of normal subjects so that less blood was pooled in the periphery.

Morphine

The place of morphine in routine treatment of pulmonary oedema has changed now that powerful and rapidly acting diuretics are available. There is no doubt that the drug usually has a beneficial effect on dyspnoea and haemodynamics. Vasko et al. (1966) demonstrated in experimental cardiogenic pulmonary oedema that administration of morphine was followed by a fall of left atrial, systemic arterial and central venous pressure, associated with a lessening of pulmonary oedema. There are several possible explanations for this beneficial effect. Systemic venous capacitance is increased, leading to a pooling of blood in the peripheries, but the magnitude of this effect seems inadequate to explain significant haemodynamic improvement (Vismara et al. 1976). The lowering of blood pressure in association with peripheral vasodilatation (Vasko et al. 1966) unloads the left ventricle. Finally the reduction of dyspnoea and induction of euphoria will decrease the work of breathing and further decrease the demands on the failing heart.

In the common context of cardiogenic shock after myocardial infarction, morphine is a life-saving drug, as well as providing essential analgesia. Diuretics carry the risk of intensifying shock by producing hypovolaemia. Infusions of hypertonic albumin may allow some decrease in oedema while blood volume is expanded.

Digoxin

Acute digitalization of patients in heart failure with pulmonary oedema is time-honoured therapy. Improvement is likely to be dramatic only in patients with uncontrolled atrial fibrillation. In the acutely sick, hypoxaemic, acidaemic and perhaps hypokalaemic patient, digoxin may produce fatal arrhythmias.

Aminophylline

This drug may be valuable for its positive ionotropic action on the heart, its synergism in the establishment of a diuresis and its bronchodilating effect. Care must be taken since it is a frequent cause of fatal arrhythmias (Camorata et al. 1971). A bolus of 6 mg/kg given intravenously over 20 minutes is safe, but subsequent doses may be hazardous unless theophylline blood levels are available (Piafsky et al. 1977). The therapeutic range of plasma concentration is narrow (10–20 μg/ml) and seemingly moderate doses may give toxic levels owing to poor metabolism of the drug in heart failure due, presumably, to poor hepatic perfusion and hepatic congestion (Piafsky et al. 1977).

Afterload reduction

A prompt and useful decrease in left atrial pressure and increase in cardiac output may be achieved by lowering systemic peripheral resistance with powerful vasodilators such as phentolamine (Majid et al. 1971), phenoxybenzamine or sodium nitroprusside (Guilla et al. 1974). Sodium nitroprusside appears to be the drug of choice for this purpose and is administered as a constant intravenous infusion. The fall in blood pressure produced is usually slight and renal function usually improves. There is a rapid relief of breathlessness and clearing of pulmonary oedema, for the duration of the infusion. Longer-term treatment with vasodilating drugs is being investigated. Successful treatment requires a simultaneous reduction of peripheral vascular resistance and left ventricular filling pressure. Prazosin (Miller et al. 1977) may be a suitable agent which combines arteriolar and venous dilatation with a cardiac sympatholytic action.

CONCLUSION

The lung is equipped with several mechanisms to prevent oedema while allowing microvascular exchange. If these mechanisms break down or are overwhelmed, the ensuing oedema may be detected at an early stage by chest radiography, but to date there are no techniques adequately to quantify the oedema. Most patients can be effectively treated with oxygen and diuretics, but the treatment of acidaemia with chronic oedema remains difficult.

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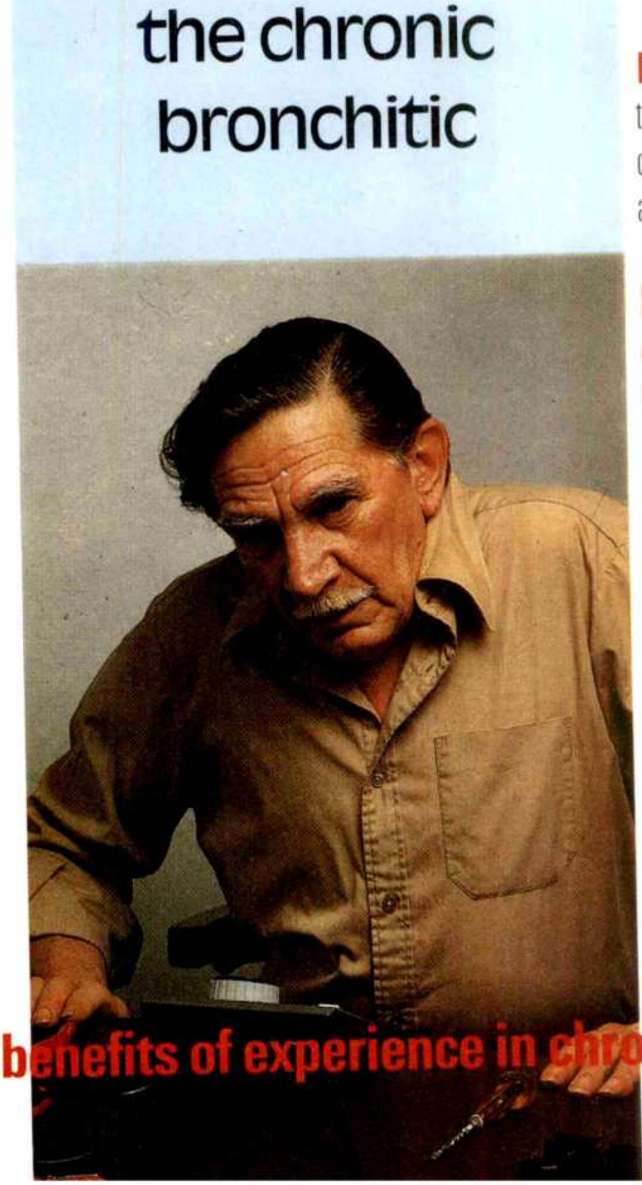

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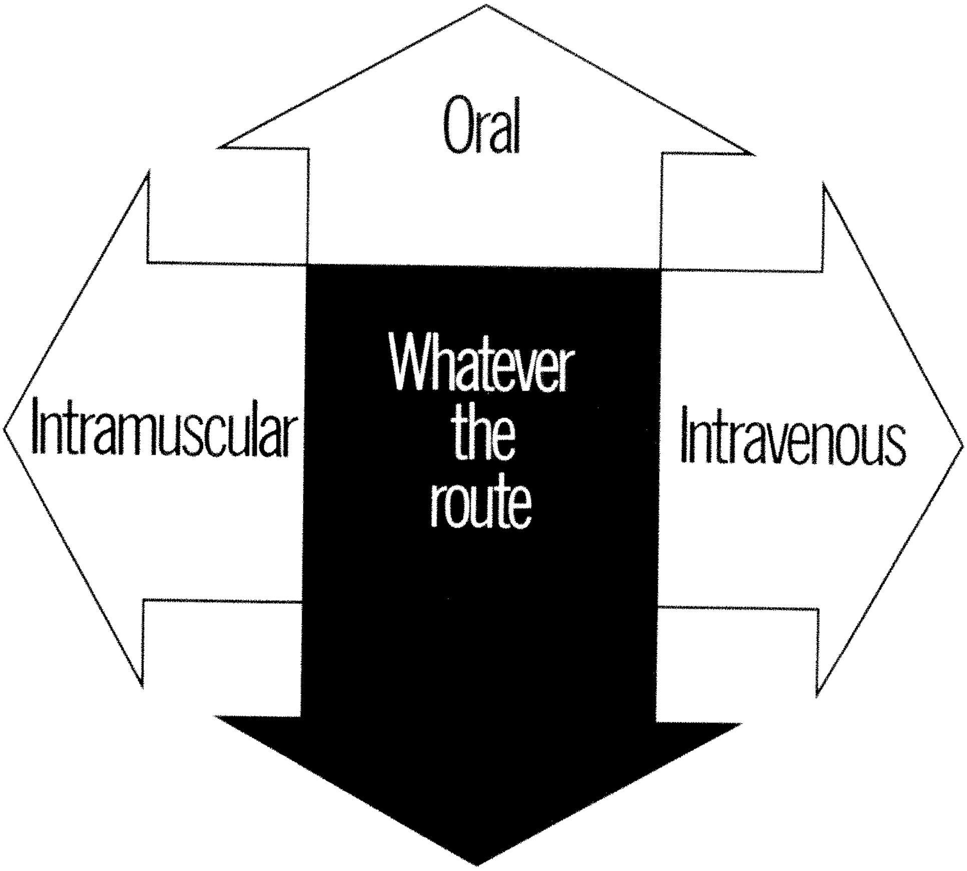

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SOUND TRANSFER FUNCTION OF THE CONGESTED CANINE LUNG

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Summary

Alterations of sound transfer function of the lung in pre-congested and congested states were studied in a canine model as an index of the accumulation of lung liquids. Pulmonary congestion was produced by graduated inflations of a balloon in the left atrium. Different degrees of pulmonary congestion were documented by post-mortem wet to dry lung weight ratios. Sound transfer function of the lung was determined utilizing passive sound transmission in the audio frequency range consisting of sinusoidal oscillations swept from 50 Hz to 2 kHz. Sound transfer function in dB was defined as 20 times the logarithm of sound output divided by sound input. These functions were computed for pre-congested and congested states of the lung and the differential values correlated with the post-mortem wet to dry weight ratios of the lung. The magnitude of sound transfer function of the lung correlated well with increasing accumulation of intravascular and extravascular lung liquids and provided a quantitative index of pulmonary congestion.

INTRODUCTION

With the description of pectoriloquy, Laennec first identified and reported alterations of sound transmission through the lung resulting from disease-induced changes in lung structure (Laennec 1818 (1962)). Only a few studies related to this phenomenon have been reported.

Characterization of the acoustic properties of the bronchial–lung–thoracic system can help in identifying varied physical states of these structures (Jackson et al. 1977; Pimmel et al. 1977). Böhme and his colleagues have measured passive sound transmission of the thorax in normal humans and in patients with a variety of pulmonary diseases (Böhme 1970*a*, *b*, 1974; Böhme & Böhme 1970, 1972; Böhme & Löw 1969*a*, *b*). These investigators have demonstrated specific modifications of sound transmission through the bronchial–lung–thoracic system in patients with pulmonary emphysema. They have attributed these changes to alterations in lung density. The accumulation of intravascular and extravascular lung liquids in congestive pulmonary oedema should also change passive sound transmission through the lung. Experimental methods have been developed to study the sound transfer function of the lung and to correlate this function with post-mortem wet to dry lung weight ratios in an experimental canine model.

Materials and Methods

Thirteen mongrel dogs weighing between 15 and 25 kg, believed to be in good health, and fasted for 12 hours were used for this study. Hair from the right hemithorax of the dogs was removed by clipping and by the application of a depilatory agent. Anaesthesia was initiated and maintained with intravenous pentobarbitone. An endotracheal tube was placed into the proximal area of the trachea and the cuff inflated. An intravenous infusion of 1.5 litres of saline or less was used during a study. At 15-minute intervals the lungs were inflated to approximately twice tidal volume.

Pulmonary venous congestion was established by means of a specially designed metal catheter with an inflatable balloon at its tip (Fig. 1). This catheter was passed through the left external jugular vein, the superior vena cava, the right atrium and, by means of atrial septum puncture, into the left atrium under fluoroscopic control. A Swan-Ganz size 7 French catheter was introduced into the right external jugular vein into a pulmonary wedge position. Placements of the catheters were checked by fluoroscopy and pressure tracings. A radiograph of an animal prepared in this manner is shown in Fig. 2.

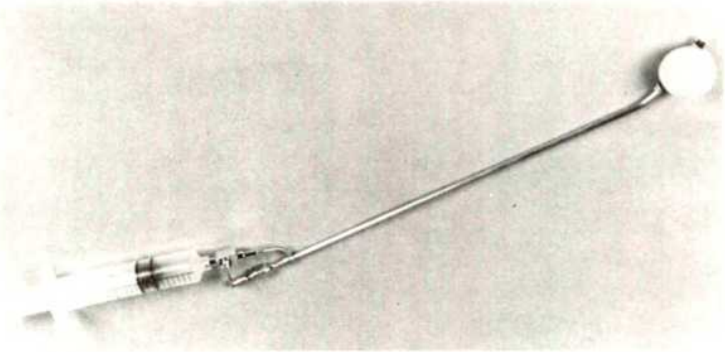

Fig. 1. Transseptal atrial catheter with inflatable balloon at tip

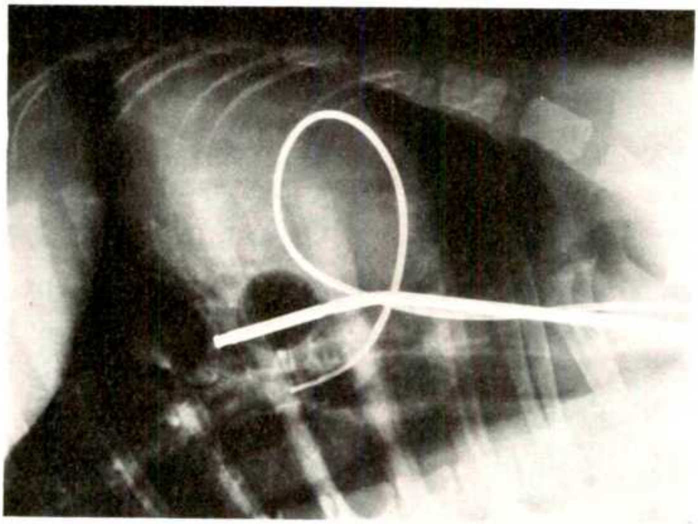

Fig. 2. Radiograph of animal with transseptal and Swan-Ganz catheters in place

After positioning the catheters, the animal was placed supine in an audio chamber (130 × 78 × 78 cm), an external shell of 1 cm plywood and lined with 10 cm of urethane foam. The Swan-Ganz catheter was connected to a Statham P23Db transducer (range 100 mmHg). This system was flushed with heparinized saline and the transducer was placed at the level of the right atrium. The endotracheal tube was extended to the exterior of the audio chamber and a Y-tube of similar diameter was attached. One of the open ends of the Y-tube was connected to a previously calibrated Hans Rudolph pneumotachograph with a Validyne MP45-2 transducer (range 10 cm H_2O). Signals from these transducers were amplified by Sanborn 1700 Series and Validyne amplifiers and displayed by means of a Brush Instrumentation Recorder, Mark 200. A 30 W Electrovoice 1828T loudspeaker driver was connected to the remaining opening of the Y-tube. This sound source was driven by a power amplifier and a Krohn-Hite Model 5100 A generator. Both input and output audio signals were detected by Sony ECM 50 electret condenser microphones, which have a frequency response of 30–14 kHz (flat within 3 dB). This microphone sensing the input signal was placed inside the Y-tube adjacent to the opening of the endotracheal tube, outside of the audio chamber and in line with the audio driver. The output signal microphone was fitted into the free end of a rubber cone approximately 1 × 2 × 3 cm. This coupling device was fitted loosely to the skin of the animal by means of adhesive over the inferior right lung field (dorsal lobe) as determined by auscultation and percussion. The unattached coupling system was previously tested in an anechoic chamber and found to have a flat response in the frequency range of 30 Hz to 3 kHz. Signals from both microphones were respectively amplified to the required levels by means of a Sony amplifier. These signals, together with signals of respiratory flow, were recorded on magnetic tape with a Tandberg four channel FM magnetic tape recorder (Model TIR 115). A block diagram of the experimental set-up is shown in Fig. 3.

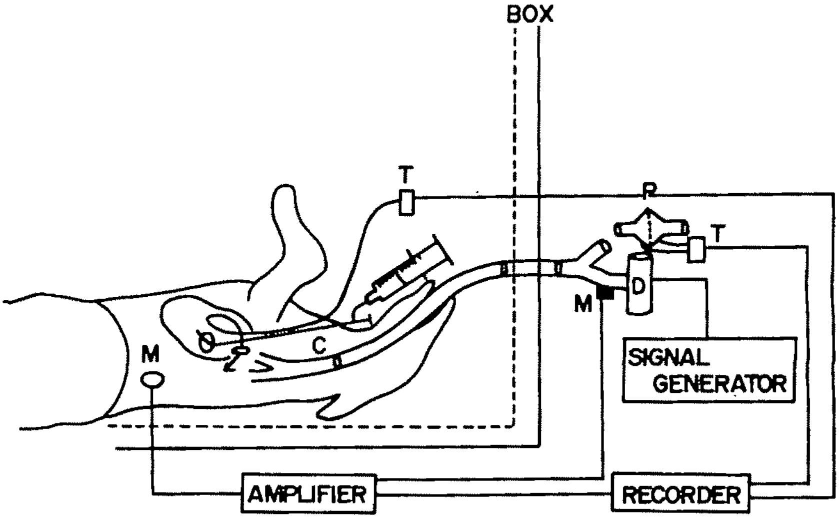

Fig. 3. Block diagram of experimental design. M = microphone, T = transducer, P = pneumotach, D = audio driver, C = catheter

After placement of the catheters and attachment of the microphones, the endotracheal tube was connected to the extension tube and the audio chamber closed. Pulmonary wedge pressure, respiratory flow and tidal volume were monitored on a chart recorder. A series of test signals were introduced into the Y-tube while adjustments were made with the audio amplifier to allow proper recording of the sounds. Once the amplification was determined, no further changes in amplification were made throughout the experiment. Pre-congestion sound transfer studies were made by inducing signals from 50 Hz to 2 kHz during a two-minute sweep. After this procedure the audio chamber was opened and the endotracheal tube disconnected from the extension tube. Varying amounts of air were then instilled slowly into the left atrial balloon to increase the pulmonary wedge pressure. Animals were studied at different ranges of pulmonary wedge pressure up to 40 mmHg. Elevations of pulmonary wedge pressure were continuously monitored and were maintained at a pre-determined level by regulation of the volume of air in the left atrial balloon. The four control animals were prepared in a similar manner, but no air was introduced into the left atrial balloon and sound transfer measurements were made at the beginning of the experiment and after two hours. During all experiments, chest auscultation using a diaphragm chest-piece of a Rieger-Bowles stethoscope was performed at five-minute intervals over the inferior (dorsal lobe) lung field adjacent to the chest microphone.

Elevation of the pulmonary wedge pressure to the pre-determined level was continued until adventitious respiratory sounds were detected. When adventitious sounds appeared, pulmonary congestion was assumed to be present. Immediately after detection of these sounds, repeat sound transfer studies were carried out as described. These results were labelled as congested lung sound transfer studies. After this study, the animal was sacrificed with euthanol and an autopsy was performed immediately after necessary experimental procedures including removal of the catheters and initiation of the autopsy.

At autopsy, the large hilar vessels were ligated and the lungs removed *en bloc*. The right lung, used for sound transfer function, was weighed immediately and the weight was identified as the wet weight of this lung. The same lung was then frozen and lypholized to a stable dry weight. Wet to dry weight ratio of the lung was established for each experiment using these weights. Previous studies in our laboratory using this method have established a normal range of wet to dry ratios of about five or below.

Sound transfer function computation was accomplished by feeding recorded sound signals from the endotracheal tube and from the chest wall into a gain-phase meter (Hewlett-Packard Model 3575A). This instrument computed and allowed display by a chart recorder the logarithmic ratio of the voltages of the detected and induced audio signals. The frequency of the sweep signal was monitored using a frequency counter. Magnitude variations of the sound transfer function were displayed on the chart recorder with simultaneous tracings of airflow and frequency information. This system allowed simultaneous recording of the logarithmic ratios of output to input sound voltages plotted at specific induced sound frequencies together with respiratory flow.

RESULTS

Post-mortem wet to dry lung weight ratios (W/D) were utilized to determine abnormal accumulation of lung liquids. This procedure has been shown to be a reliable method of detecting pulmonary congestion in canine lungs (Guyton & Lindsey 1959). Pulmonary congestion was produced by obstruction of blood flow in the left atrium. The resulting elevations of pulmonary wedge pressures were monitored, allowing changes in the size of the atrial balloon and the degree of atrial obstruction thus giving a range of steady state pulmonary wedge pressure elevations which resulted in wide spectrum of W/D found at post-mortem.

The interrelationship between the input and output signals is described by a sound transfer function (T) defined as:

$$T = 20 \log \frac{V_D}{V_I} \ (\mathrm{dB})$$

V_I refers to the voltages of induced signals, and V_D refers to voltages of recorded signals detected over the inferior chest wall. Representative plot of the sound transfer function of the lung is shown in Fig. 4. The transfer function of sound, expressed in decibels, is plotted on the vertical axis as a logarithmic function of the ratio of output to input sound

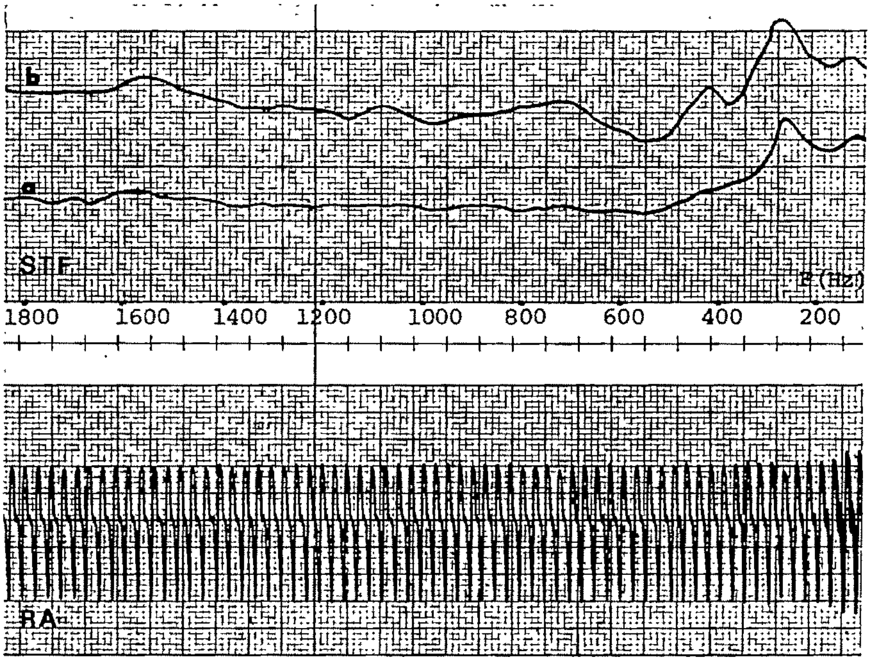

Fig. 4. Tracing of sound transfer function (STF) for pre-congested (a) and congested states (b) with corresponding respiratory airflow (RA)

intensity. Tracing a represents the sound transfer function in the pre-congested state, and tracing b demonstrates the sound transfer function when pulmonary congestion was present. Time as well as frequencies of induced sound are plotted on the horizontal axis. This demonstrates the two-minute sweep of the induced audio signals. A relatively long sweep of the induced signals was designed to minimize alterations in sound transmission resulting from changes in lung size and respiratory air-flow during the respiratory cycle to an insignificant degree. Furthermore, these minimal variations in sound transfer due to effect of air-flow within the bronchial tree during respiration were filtered out electronically to represent average values of sound transmission. Respiratory flow as recorded from the endotracheal tube is also shown on these tracings. The induced and recorded sound signals were much louder than cardiovascular and respiratory sounds.

Congestion of the lung with an increase in intravascular and extravascular fluids altered the sound transfer function of the lung by increasing transmission of the sound through the bronchial–lung–thoracic system. An average of the ratios of sound transmission taken at 100 Hz intervals over the entire range (50 Hz to 2 kHz) was designated T_E for congested states of the lung and T_N for conditions before congestion. T_D represents the increase in transfer function of the lung through the bronchial–lung–thoracic system in congested lungs compared to non-congested lungs. Sound transfer functions of the lung expressed as T_D correlated with the post-mortem wet to dry lung weight ratio (W/D) as shown in Fig. 5. The W/D ratio is plotted on the vertical axis. Each point represents the results of one experiment involving one animal. There was no change in sound transmission in control animals without an increase over normal of

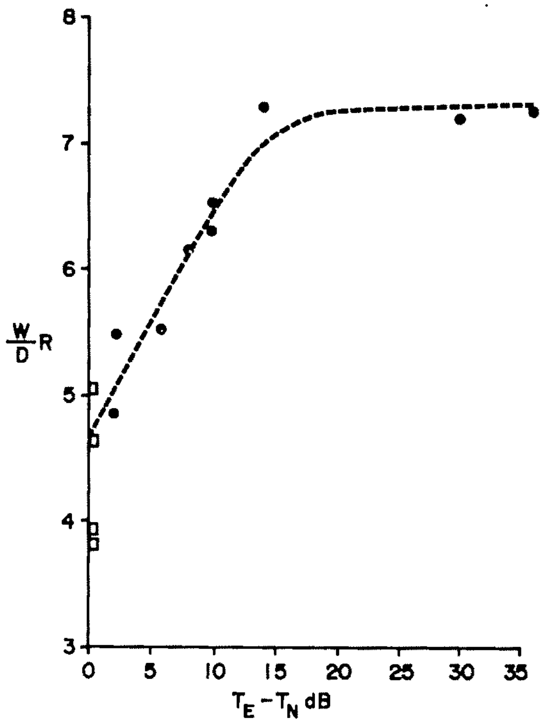

Fig. 5. Interrelationship of post-mortem wet to dry weight ratios W/D and differential sound transfer function of congested lungs (T_D), T_N = sound transfer function of pre-congested lungs, T_E = sound transfer function of congested lungs

post-mortem W/D lung weight ratios. Control animals, as identified, demonstrated W/D lung ratios about five or below and did not have increased transfer of sound after a two-hour period. An increase in intravascular and extravascular lung liquids, as detected by an increase in W/D lung ratios, resulted in an increase in sound transferred through the bronchial–lung–thoracic system. The results show a linear region of dependence between T_D and W/D lung ratios up to seven and demonstrate a fundamental relationship between these functions within this range.

Although saturation of this function is seen at W/D values above seven and is believed to be a result of alveolar flooding, the linear position of this relationship provides information within a significant range which should allow important clinical correlations. This phenomenon also reveals the high sensitivity of this technique.

DISCUSSION

Physical properties of different components in the bronchial–lung–thoracic system affect the reflection, absorption and transmission of sound. Respiratory sounds generated within the respiratory airways and passive sounds induced in the airways are modified in their frequency, intensity, quality and duration by the acoustical properties of the various structures in this system. The bronchial–lung–thoracic system may be considered a multi-layer acoustic structure composed of media of various acoustic impedances. Specifically, airways and alveolar spaces may be considered as low-density heterogeneous media, while high-density heterogeneous media include vessels, tissues and bones. To a large extent tissue fluid will determine the fundamental frequencies and harmonics peculiar to the tissue and increased fluid content in tissue results in an increase in high-frequency components. The variations in the natural frequencies of different components and the variations in phase shifts of sound resulting from changes in the propagation of signals at different velocities through these structures affect the final composition of the detected signals. Intensity of the sound at different frequencies perceived over the lung fields is affected by the anatomical structure in both the normal and the abnormal state of the bronchial–lung–thoracic system. Acoustical impedances due to the viscosities of these media account for conversion of part of the sound energy into heat. Reflection of sound at boundaries of different acoustical impedance represents most of the lost energy and contributes to the reduced intensity of detected sound. In general, the amplitude of vibration is inversely proportional to the stiffness of this system at a given induced force. Intensity of the sound is also inversely proportional to the square of the distance in a homogeneous medium, although in a medium such as the bronchial–lung–thoracic system, this relationship is more complex. Furthermore, variations in sound conductivity are also related to the changes in stiffness during the respiratory cycle, including changes in the thickness of the chest wall, volume of the lung, and displacement of thoracic structures in relation to the recording sensor.

Theoretical and physical interpretations of intrathoracic passive sound transfer of the thorax were discussed in depth (Böhme 1970 *a*, *b*; Böhme & Böhme 1970; Böhme & Löw 1969*a*, *b*). The bronchial–lung–thoracic system was characterized by these investigators as a second-order system with mass and elasticity of significant meaning and friction as a negligible factor. They concluded that alterations in passive sound transmission were significantly related to the variations in the density and elasticity of lung structure. In the studies referred to induced and recorded signals were selectively filtered to allow determination of one preselected sound frequency. Twelve discrete frequencies at six sites over the lung fields of 12 human subjects, including normal subjects and patients with chronic bronchitis, asthma and pulmonary emphysema were studied. It was shown that there was an obvious attenuation of high-frequency sound transmission through the bronchial–lung–thoracic system in patients with pulmonary emphysema and concluded that the changes were related to the density and elasticity of the emphysematous lung.

Freyschmidt (1960) and Freyschmidt and Kaiser (1960) also studied passive sound transmission of the bronchial–lung–thoracic system by inducing sound over the frequency range up to 500 Hz in the mouth and recording it from the posterior chest wall of human subjects. The particular frequency characterized by minimal attenuation of transmitted sound was interpreted as the fundamental frequency of the entire system. Patients with pulmonary or cardiovascular disease were not studied. Ploy-Song-Sang et al. (1977) induced white noise in the upper airways of patients and showed the transmission of sound to the chest wall was dependent on regional lung volume.

The present study of sound transfer function of the canine lung in pre-congested and congested states revealed a considerable increase in the transmission of audible sound through the lung associated with an accumulation of lung liquids as demonstrated by post-mortem W/D ratios. This occurred in lungs which demonstrated only minimal increases in post-mortem W/D ratios and the absence of alveolar flooding. The increase of sound transmission occurred throughout the studied spectrum of sound and the degree of increase was greater at high frequencies. The increase in sound transmission with only a minimal increase in intravascular and extravascular lung liquids reveals the sound transfer function to be very sensitive to these changes in structure of the lung. Chest wall oedema and pleural effusion did not occur in these animals, and thus such changes could not account for the alteration of sound transmission. A decrease in lung size is expected to occur with increasing lung liquids, but this too would result in increased density of the lung and should have a direct relationship with congestion. These studies together with the studies cited above imply that the sound transmission through the lung is significantly dependent on the lung density.

This technique of providing an index of the magnitude of pulmonary congestion could assist in following changes in the volume of lung liquids in the congested human lung. It has the advantages of being safe, non-invasive and rapidly repeatable. As already mentioned, diagnostic methods including chest auscultation, chest radiographs and haemodynamic invasive studies have certain limitations in studying pulmonary oedema. This method could be adapted to clinical use and could prove helpful in following lung liquids in patients with acute and chronic heart failure. Since these changes in sound transfer function of the lung depend on lung density, this method may also serve to identify emphysema or connective tissue diseases even in an early stage.

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INTRANASAL FLUNISOLIDE, PLACEBO AND BECLOMETHASONE DIPROPIONATE IN PERENNIAL RHINITIS

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Summary

Flunisolide nasal spray has been compared with placebo and with beclomethasone dipropionate in the treatment of perennial rhinitis.

A double-blind, cross-over study in 26 patients comparing intranasal flunisolide (total dose 300 μg/day) with placebo showed superiority of the active preparation in the relief of sneezing, stuffiness and runny nose. Physicians and patients significantly preferred the active spray. Side-effects on both sprays were mainly confined to transient nasal irritation. Plasma cortisol levels did not change significantly during the trial.

A single-blind, cross-over study in 34 patients comparing flunisolide and beclomethasone dipropionate showed relief of sneezing, stuffiness, runny nose and nose-blowing with both medications. There were no differences between the effects of the two preparations. Physicians and patients favoured the drugs equally. Side-effects were minor.

Introduction

Corticosteroids have been shown to relieve the symptoms of perennial and seasonal allergic rhinitis. Local application of the drug to the nasal mucosa is preferred to systemic administration because smaller doses can be effectively used. Topically applied steroids tried in allergic rhinitis include hydrocortisone (Herxheimer & McAllen 1956), dexamethasone (McAllen & Langman 1969), betamethasone valerate (Brostoff & Czarny 1969) and beclomethasone dipropionate (Brown et al. 1977). Despite the local application adrenal suppression is possible. This has been shown after use of dexamethasone nasal spray. A prompt return of adrenal function was seen after withdrawal of the drug (Norman et al. 1967).

Flunisolide, a synthetic corticosteroid, used intranasally, has been favourably compared with placebo in the treatment of perennial allergic rhinitis (Bloom et al. 1977) and seasonal allergic rhinitis (Turkeltaub et al. 1976; Kammermeyer et al. 1977). In the two studies where adrenal function was measured no important effects were seen. The purpose of the present trial was to compare flunisolide nasal spray with placebo and with beclomethasone dipropionate aerosol in patients suffering from perennial rhinitis.

Materials and Methods

Men and women between the ages of 16 and 60 years suffering from perennial rhinitis with or without seasonal exacerbations were entered into the trial. The trial took place during a time when symptoms were not subject to fluctuation. Pregnancy, illnesses in which systemic corticosteroids are contraindicated and nasal obstruction due to polyps were criteria for exclusion from the trial. Also excluded were patients taking antihistamines for reasons other than perennial rhinitis and patients who had received either intranasal steroids or sodium cromoglycate within the month before admission into the trial or oral steroids within three months of starting the trial. Patients with asthma were allowed to continue with any established therapy as long as medication continued unchanged during the trial. Patients volunteered for the trial after full explanation by the clinician.

On entry to the trial assessments were made of the severity of sneezing, stuffiness, runny nose, nose-blowing and post-nasal drip. Each symptom was recorded as none (0), mild (1), moderate (2) or severe (3). Patients were asked whether symptoms interfered with routine life or sleep. An examination of the nasal mucosa and nasal secretions was made. Patients were asked to keep a daily record of symptoms. At each follow-up visit these assessments were repeated and in addition patients and physicians assessed the overall control of symptoms. Side-effects were elicited by indirect questioning. At the end of the trial patients and physicians indicated a preference for one of the study medications.

At admission and follow-up visits blood was taken for estimation of haemoglobin, eosinophils and cortisol. A nasal swab was taken for detection of *Candida* growth.

Part I was a double-blind, cross-over study of flunisolide nasal spray and the vehicle alone. Patients used each spray for four weeks. Flunisolide was provided as a 0.025% aqueous solution in a bottle fitted with a metered pump. The dosage was two actuations (25 μg/actuation) into each nostril three times a day.

Part II was a single-blind, cross-over comparison of flunisolide and beclomethasone dipropionate. Patients were asked not to reveal details of the physical characteristics of the medication to the physician. Flunisolide was given as two actuations of aqueous spray into each nostril twice daily (200 μg/day). Beclomethasone dipropionate was given as one actuation of the pressure-packed aerosol into each nostril four times a day (400 μg/day).

RESULTS

Part I

Twenty-six patients, 11 men and 15 women (age range 14 to 57 years), were entered. All had moderate to severe symptoms for one to 23 years and nine suffered seasonal exacerbations. Seventeen of the patients showed a positive reaction in the prick skin test to one or more of the common allergens tested. The most common allergen was house dust.

Changes in mean symptom scores are shown in Fig. 1. The active spray was superior to placebo in relieving sneezing ($P=0.015$), stuffiness ($P=0.004$) and runny nose ($P=0.035$). There were no statistically significant differences between the effect of active and placebo sprays on nose-blowing and post-nasal drip. Interference with routine life and sleep was reduced by both sprays. No pathological changes in the nasal mucosa were seen and both sprays tended to reduce the amount of nasal secretions. At the end of the study both patients and physicians showed a statistically significant preference for flunisolide ($P<0.05$) (Table I).

Twelve patients reported side-effects on the vehicle and ten on flunisolide. The most common side-effect was transient nasal irritation following the use of the spray. This was reported by seven patients using flunisolide and eight patients using placebo. Two patients did not complete the trial; one withdrew because of occipital headache while using the placebo spray and one withdrew for social reasons while using the active spray. Haemoglobin, blood eosinophils and plasma cortisol levels showed no statisti-

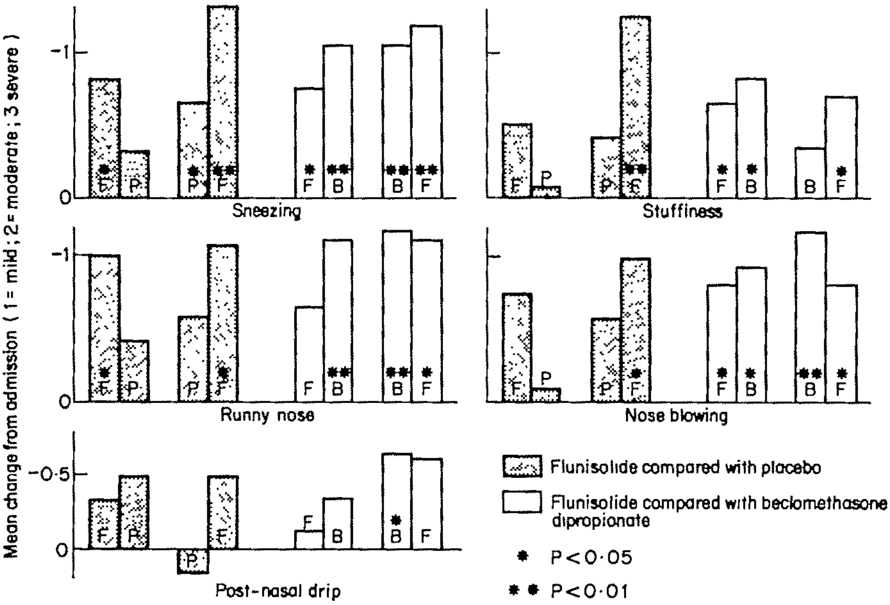

Fig. 1. Mean changes in various symptom scores. F = flunisolide; B = beclomethasone dipropionate; P = placebo. * $P<0.05$; **$P<0.01$ (Wilcoxon sign-rank test)

Table I. Medication preferences

Medication	*Patient*	*Physician*
Part I		
Flunisolide	15	16
No preference	4	2
Placebo	4	5
P	0.03	0.03
Part II		
Flunisolide	15	13
No preference	4	4
Beclomethasone dipropionate	14	15
P	NS	NS

cally significant changes during the trial. *Candida* growth was not detected in the nasal secretions.

Part II

Thirty-four patients, 16 men and 18 women (age range 19 to 58 years), were entered into the trial. All had moderate to severe symptoms of six months' to 50 years' duration and seven suffered seasonal exacerbation. Twenty-two of the patients showed a positive reaction in the prick skin test. House dust, house dust mite and plant materials accounted for most of the positive results. Mean changes in symptom scores are shown in Fig 1.

Both sprays produced statistically significant reductions from admission values in sneezing, stuffiness, runny nose, nose-blowing and interference with routine life. No statistical difference could be shown between the effects of the two drugs. Macroscopical examination of the nasal mucosa showed no pathological changes and nasal secretions tended to be reduced.

A comparison of the physicians' assessment of the control of symptoms by each therapy is shown in Table II. Both drugs produced good to total control in over 20 of the 34 patients. Physicians' and patients' preference for the medication is given in Table I; the two medications were equally favoured. Side-effects were reported by 13 patients while on flunisolide and eight patients while on beclomethasone dipropionate. Side-effects were minor and mostly confined to nasal irritation or dryness.

Table II. Achievement of nasal sprays

Control of symptoms	*Flunisolide*	*Beclomethasone dipropionate*
Worse	—	—
None	5	2
Minor	7	8
Good	17	20
Complete	4	3

In individual patients, flunisolide was better than beclomethasone dipropionate in seven patients, worse in seven and equal in 19.

One patient discontinued using flunisolide because of mild but persistent nose bleeds and another patient stopped using beclomethasone dipropionate because of a feeling of tiredness and apathy. A further two patients failed to complete the trial, one patient because of lack of efficacy on flunisolide and one who failed to return for a follow-up visit.

No significant changes in plasma cortisol values were seen between admission and follow-up visits. *Candida* growth was not detected in the nasal secretions during either drug therapy.

DISCUSSION

This trial has shown that flunisolide is superior to placebo in controlling the symptoms of perennial rhinitis and equal in efficacy to beclomethasone dipropionate. The first part of the trial demonstrated the importance of a comparison with placebo; many of the patients showed a good response to the placebo spray. It is conjectured that the propylene glycol content of the vehicle may be responsible. However, the active spray showed significant superiority over placebo in the relief of sneezing, stuffiness and runny nose and was significantly preferred by both doctors and patients. Side-effects were minor and no macroscopical adverse changes in the nasal mucosa were seen.

The comparison of flunisolide with beclomethasone dipropionate showed no difference between the preparations. The efficacy of beclomethasone dipropionate is well documented. In this trial both drugs showed a high degree of efficacy and did not interfere with adrenal function. One difference between the two preparations used in this trial was the delivery system; flunisolide was administered in aqueous solution delivered by a metered pump while the beclomethasone dipropionate was delivered from a pressure-packed aerosol canister.

Flunisolide is a useful addition to the limited number of drugs used to control rhinitis.

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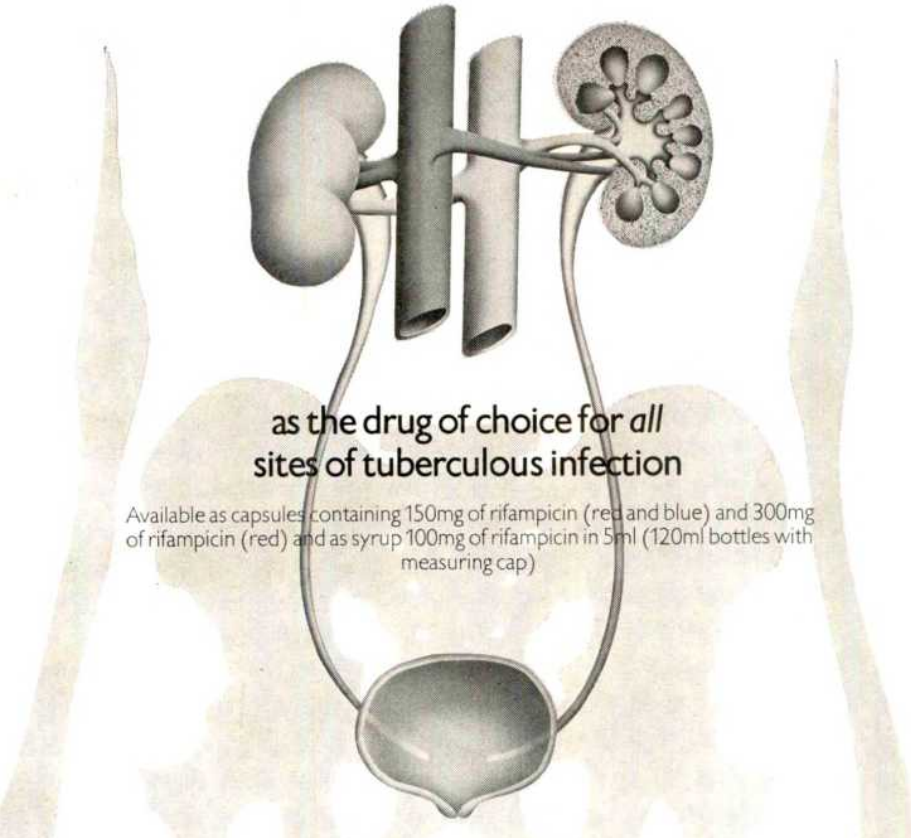

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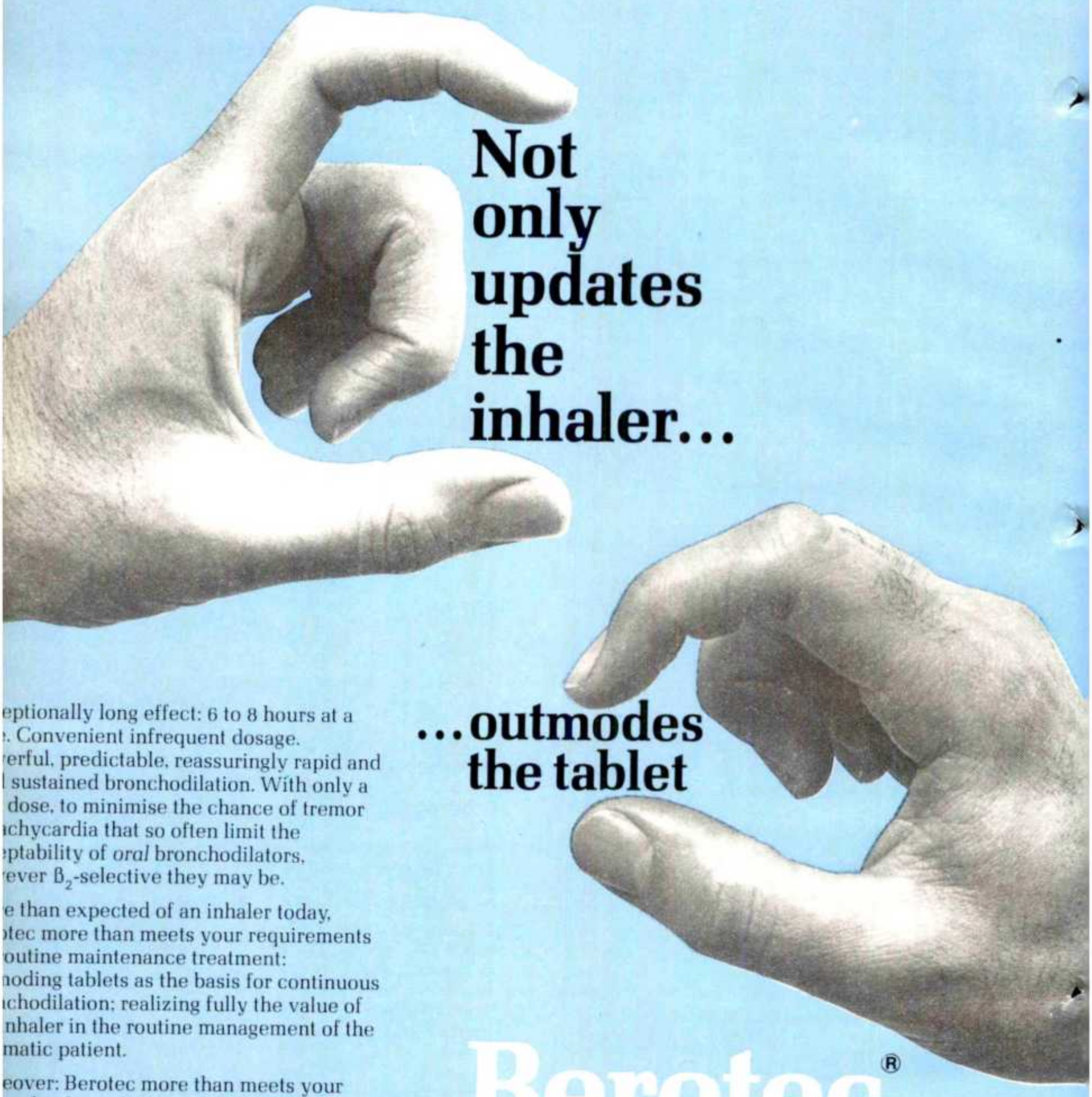

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ACUTE EFFECTS OF SMOKING A SINGLE CIGARETTE ON THE AIRWAY RESISTANCE AND THE MAXIMAL AND PARTIAL FORCED EXPIRATORY FLOW VOLUME CURVES

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AND T. J. H. CLARK

Guy's Hospital, London

Summary

The acute airway response to smoking a single cigarette was assessed in eight symptom-free male smokers. The changes in airway function were determined using a computer analysis of maximal and partial expiratory flow volume curves together with measurement of airway resistance. The amount of smoke inhaled was assessed by measuring levels of nicotine in venous blood.

When the results of all studies were analysed for the group as a whole only small and inconsistent changes in airway function were observed after smoking a cigarette, although all the subjects appeared to inhale the smoke.

Although the group showed inconsistent changes, one subject exhibited a change on all four occasions in the studies using the maximal and partial expiratory flow volume curves. This was seen particularly for $\dot{V}max_{50}$ and $\dot{V}max_{40}$ obtained from the maximal and partial expiratory flow volume curves respectively. There appeared to be no difference between the two manoeuvres in their sensitivity to smoke-induced change. One subject showed a response to smoking when airways resistance was measured but this was on only one of two occasions. It is therefore possible that certain smokers are more susceptible to inhaled cigarette smoke and such individuals may be those who develop chronic airflow obstruction.

The absence of a group effect was attributed to any smoking response being smaller than the other factors which affect measurements of airway function.

INTRODUCTION

The inhalation of irritant gases, dusts and aerosols may result in a vagally mediated reflex bronchoconstriction and tachypnoea (Widdicombe & Sterling 1970). Cigarette smoke was been considered such an irritant (Nadel & Comroe 1961; Sterling 1967). In man, many studies using indirect measurements of airway calibre have shown apparent airway narrowing after smoking a single cigarette. However, in those studies involving large numbers of smokers not only is there a large variation in the size of the response to smoke inhalation but only a proportion of smokers actually appear to respond with bronchoconstriction (Guyatt et al. 1970; McDermott & Collins 1965). As there may be a link between such responders and the liability to proceed to develop chronic obstructive bronchitis, we undertook a preliminary study to see if there were important. differences in the way in which individual smokers responded to inhaled cigarette smoke For this we used a small group of young male smokers without symptoms who smoked low-tar filtered cigarettes. To determine whether our cigarette smokers actually inhaled the smoke, we measured venous blood nicotine before and after smoking (Russell et al. 1975) and obtained a record of the number of drags taken from the cigarette (McDermott & Collins 1965). The changes in airway calibre were assessed from derivatives of a forced exhalation flow–volume curve and from determinations of airways resistance.

Materials and Methods

Eight male smokers between 20 and 30 years old, who habitually inhaled cigarette smoke and complained of no respiratory symptoms, were recruited. All had smoked for at least five years but none more than eight pack-years (a pack-year equals 20 cigarettes per day for one year).

In order to decide upon the most sensitive index of change in airway calibre two studies were undertaken; four subjects were selected for each. The first used the forced exhalation manoeuvre into a dry spirometer (Ohio 840) which was on-line to a mini-computer to analyse flow and volume signals simultaneously. The second used standard determinations of inspiratory resistance in a constant-volume whole-body plethysmograph (Dubois et al. 1956), the transducer signals being recorded on an X-Y recorder (Bryans 26000). In the forced exhalation study, the amount of smoke inhaled was assessed from changes in nicotine level of venous blood taken before and two minutes after smoking. This was subjected to gas–liquid chromatography analysis for nicotine levels (Feyerband et al. 1975). The same type of cigarette was smoked in each study, being a low tar (Department of Health and Social Security 1976) filtered cigarette, with a nicotine yield of 1.01 mg/cigarette. The number of 'drags' of smoke taken from each cigarette was recorded in both studies. The subjects were encouraged to adopt their own 'natural' manner of smoking, taking on average 10 minutes to smoke a cigarette.

Two types of forced exhalation test were used: the standard maximal forced expiratory flow volume curve (MEFV) (Hyatt & Black 1973) and a partial forced expiratory flow volume curve (PEFV). The latter was carried out because full inhalation to total lung capacity (TLC) may reduce the degree of bronchoconstriction (Nadel & Tiernay 1961) and might, therefore, mask changes induced by cigarette smoke. To obtain this curve the subject first inhales to TLC then exhales quickly but not forcibly to 80% of the vital capacity (VC) holding his breath for 15 seconds to allow return of bronchomotor tone before completing the forced exhalation (Green & Mead 1974). From these two flow–volume curves a number of variables were obtained by the mini-computer (Table I).

As bronchial reactivity may exhibit a diurnal variation (DeVries et al. 1962) the subjects smoked four cigarettes, two in the morning and two in the afternoon. There was an interval of at least 90 minutes between each to avoid the effects of one cigarette interfering with another (Nadel & Comroe 1961). In one morning and one afternoon study MEFV was used to determine the effect of smoke inhalation and in the other two studies PEFV was used.

In an attempt to avoid observer bias and lessen the effect of suggestion upon the measurement of airways resistance in the body box study (Spector et al. 1976), each subject performed four studies but cigarettes were smoked in two only: one in the morning and one in the afternoon and at least 90 minutes after an earlier cigarette. In the other two experiments a period without smoking was included as a control but with the same series of measurements of airways resistance. In both control and smoking studies, the subjects performed the airways resistance measurements without any preceding full inhalation or exhalation. Three separate observers, who did not know whether the subject had smoked or not, assessed the slopes of the X-Y record obtained from the body plethysmograph to provide separate records of airways resistance and lung volume. The calculations of airways resistance (R_{aw}) and lung volume (V_{tg}) and other derived variates which

Table I. Variables measured from the expiratory flow–volume curves

MEFV	*PEFV*	
VC	VC	Vital capacity
$FEV_{1.0}$		Forced expired volume in 1 second
FER		Forced expired ratio
$Vmax_{25}$		Maximal flow at 25% of vital capacity
$Vmax_{40}$	$Vmax_{40}$	Maximal flow at 40% of vital capacity
$Vmax_{50}$	$Vmax_{50}$	Maximal flow at 50% of vital capacity
$Vmax_{75}$	$Vmax_{75}$	Maximal flow at 75% of vital capacity
PEFR		Peak expired flow rate
TTPF		Time to peak flow
TTNF		Time to no flow
Mean flow 25–75%	Mean flow 25–75%	Mean flow between 25–75% VC
Mean flow 40–80%	Mean flow 40–80%	Mean flow between 40–80% VC

MEFV = maximal expiratory flow–volume curve.
PEFV = peak expiratory flow–volume curve.

correct for variations in lung volume (for example specific airways resistance and specific airways conductance) were calculated in the standard fashion.

In both the body box and forced exhalation studies, triplicate 'pants' and 'blows' were performed at intervals of ten minutes. Three sets of measurements were made before smoking and were repeated two minutes after smoking and at 10-minute intervals up to 80 minutes after the smoking challenge. This provided information on both timing and duration of any smoke-induced response.

The studies yielded a large number of results: 12 from the MEFV, six from the PEFV and six from the body box study. Each result was analysed separately using factorial analysis of variance (Armitage 1971) and to perform the computations the Genstat 307 statistical language (Rothamstead Research Station) was employed using the University of London Computer Centre computer.

The significance of certain main effects (or factors) were analysed and related to individual measurements. For example, in the forced exhalation studies the main effects were:

1. The effect of the 10-minute intervals of time between triplicates.
2. The effect of the time of day.
3. The effect of different subjects.

The background or residual variation of each measurement was taken from the variation within triplicates.

A similar experimental design was also used in the body box analysis but included a combined analysis of control data and observer bias.

When considering the significance of the main effects and their interactions only P values of less than 0.0043 in the MEFV study or 0.0085 in the PEFV and body box studies were accepted. These reduced P values lessen the chances of accepting falsely positive results when numerous measurements have been made. This is equivalent to a P value of 0.05 for each measurement (Kirk 1968).

When comparing post-smoking measurements with pre-smoking controls, a multiple comparison technique of Dunnet (1964) was used to provide a 95% confidence interval, which is proportional to the residual variation of each measurement under consideration.

RESULTS

When considering the MEFV study as a whole, there was no overall response due to smoking in any of the 12 variables. Examples for the $FEV_{1.0}$, $\dot{V}max_{40}$ and $\dot{V}max_{50}$ are shown in Fig. 1 and none of the post-smoking values were significantly different from the controls. However, for certain variables significant interaction was observed between subject and interval of time ($P < 0.0043$), implying that some subjects behaved differently during the study. For example, Subject 1 showed an immediate response to smoking, whereas the other subjects did not (Fig. 2), with the $\dot{V}max_{50}$ measurement.

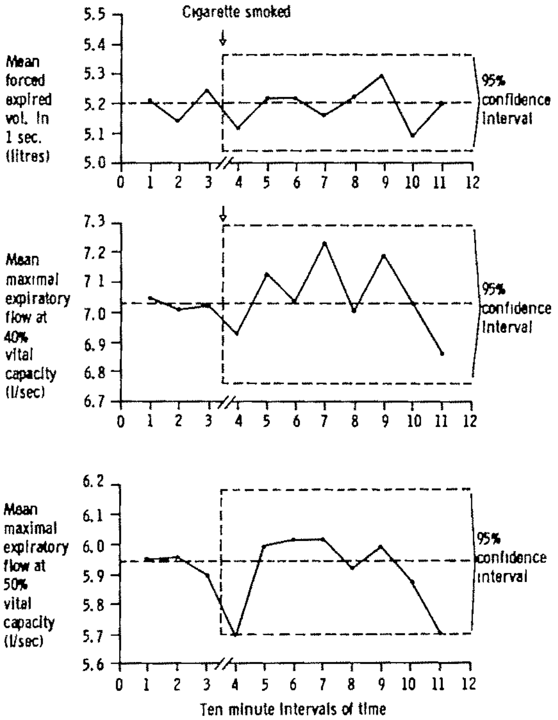

Fig. 1. Examples of FEV$_{1.0}$, $\dot{V}max_{40}$ and $\dot{V}max_{50}$ obtained from the MEFV. Each point represents the mean results of all the subjects on both occasions of smoking. As will be seen, none of the post-smoking means are different from the controls at a 5% level of significance

In the PEFV study as a whole, only $\dot{V}max_{40}$, of the six variables examined, indicated an acute airway response to smoking (Fig. 3). However, as in the MEFV study, there was significant interaction (P value less than 0.0085) between the factors, subjects and intervals of time, implying that subjects again behaved differently during the study. For $\dot{V}max_{40}$ Subject 1 again showed an immediate response following smoking, unlike the other subjects (Fig. 4) and the apparent group effect may thus be accounted for by only one subject. Indeed, Subject 4 showed a late bronchodilatation after smoking. There was no diurnal variation in either the MEFV or PEFV studies as the effect of the time of day factor produced no significant interaction for any of the measurements ($P > 0.0043$ and 0.0085 respectively).

The four subjects inhaled similar amounts of tobacco smoke during both MEFV and PEFV studies as assessed by the change in level of nicotine in venous blood (Table

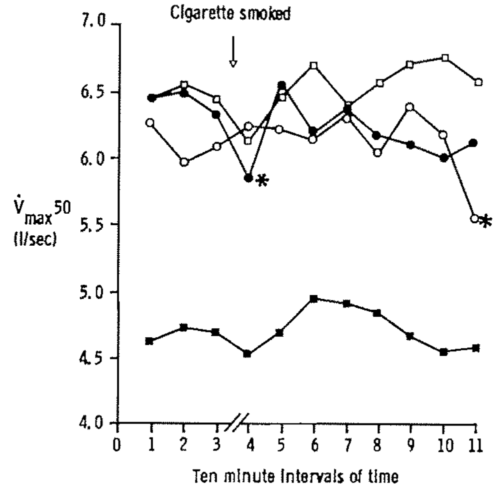

Fig. 2. The individual subjects' results for $\dot{V}max_{50}$ in the MEFV study (Subject 1 ●, Subject 2 ○, Subject 3 ■, Subject 4 ☐). Only Subject 1 shows an immediate reduction after smoking. Subject 2 showed a late fall in $\dot{V}max_{50}$ which we have assumed to represent a fatigue phenomenon. * indicates a significant difference from control at 5% level

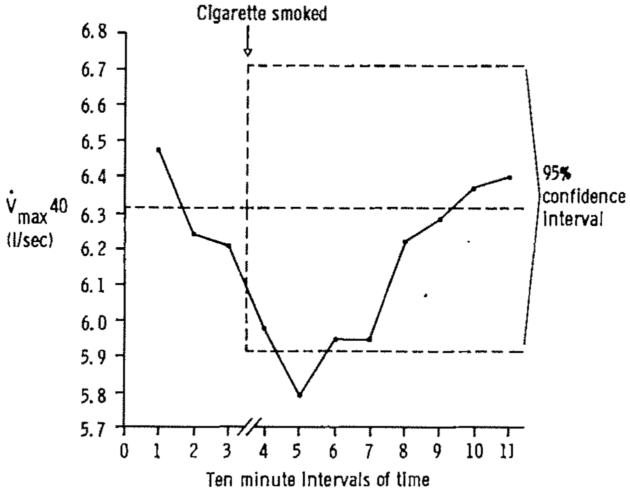

Fig. 3. The mean results for all subjects for both cigarettes in the PEFV study showing $\dot{V}max_{40}$ with an apparent reduction following smoking

II). In particular, Subject 1 did not appear to inhale more smoke, nor did he take more 'drags' from the cigarettes than the other subjects.

If smoking were to produce an acute response in the body box study it would be expected that there would be an increase in the difference between the smoking and control experiments following smoking. This was not seen in any of the variables and in particular there was no increase in airways resistance (R_a). Indeed, specific airway conductance (S_{gaw}), a measurement commonly used to compensate for variation in lung

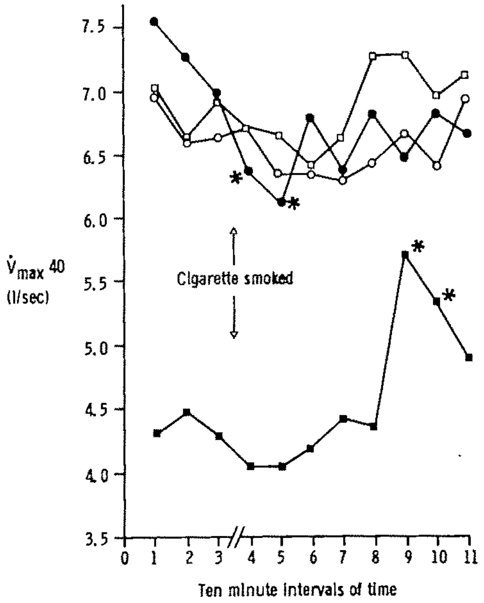

Fig. 4. The individual results from the PEFV study for $\dot{V}max_{40}$ (Subject 1 ●, Subject 2 ○, Subject 3 ■, Subject 4 □). (The morning and afternoon studies are combined.) Subject 1 again shows a significant reduction immediately after smoking. * indicates a significant reduction from the control at a 5% level

Table II. Change in level of venous blood nicotine (nmol/litre) after each cigarette in 'forced exhalation' studies and number of 'drags' taken

Subject		*MEFV*		*PEFV*	
		Change in venous blood nicotine	No. of drags	Change in venous blood nicotine	No. of drags
1	a.m.	4.77	10	4.00	11
	p.m.	5.51	10	3.77	11
2	a.m.	9.89	11	10.10	10
	p.m.	9.29	10	9.55	10
3	a.m.	3.54	14	8.50	14
	p.m.	8.27	15	4.98	15
4	a.m.	4.47	7	5.79	8
	p.m.	4.78	7	4.13	7

volume (Guyatt et al. 1967), showed an improvement after smoking (Fig. 5). However, there were again differences between the subjects in their responses as judged by the interaction between subject and interval of time. Only Subject 6 in the afternoon study showed an increase in airway resistance (R_{aw}) which could not be accounted for by variations of lung volume (Fig. 6).

As in the forced exhalation studies, the subjects took a similar number of 'drags'

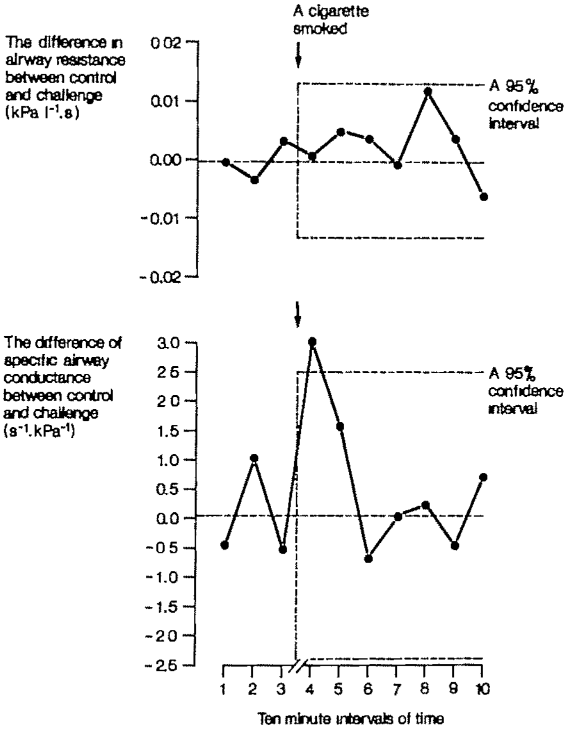

Fig. 5. Airways resistance (R_{aw}) and specific airways conductance (S_{gaw}), showing the difference between the challenge and control experiments (challenge – control mean values at each time interval). No effect of smoking was observed when considering R_{aw} in all subjects, but it appeared that there was an improvement in S_{gaw} after smoking

from the cigarettes in the morning and afternoon studies. (Subject 5 = 9 and 8, Subject 6 = 10 and 10, Subject 7 = 9 and 9 and Subject 8 = 10 and 9 'drags'.)

Although three observers recorded different absolute values for airways resistance (R_{aw}) and lung volume (V_{tg}), there was no significant interaction between observers and the other main factors ($P > 0.0085$), that is each observer recorded the same changes.

DISCUSSION

From the many earlier studies in this field, there appear to be two separate views on the acute effects of smoking on the lung. There are those workers who consider that acute bronchoconstriction invariably follows the inhalation of cigarette smoke (Nadel & Comroe 1961; Sterling 1967; Hamosh & Da Silva 1977; Sobol et al. 1977). Others studied large numbers of smokers and concluded that only a proportion exhibit a significant response to smoking (McDermott & Collins 1965; Guyatt et al. 1970; Clarke et al. 1970). In one study (Robertson et al. 1969) only 24 of 91 heavy smokers were considered to be responders to cigarette smoking. Our findings of no consistent overall response and of significant bronchoconstriction in only two subjects appear to be in keeping with the view that only a proportion of smokers respond to cigarette smoke.

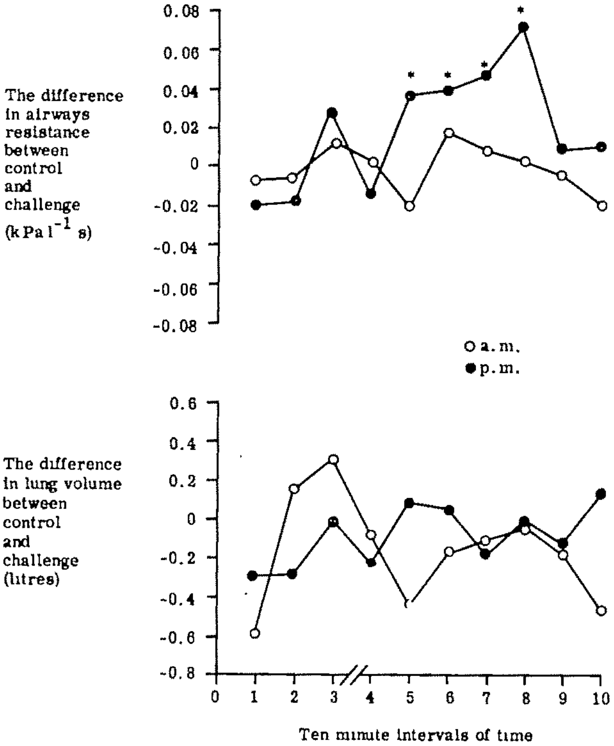

Fig. 6. The results of the morning and afternoon studies for Subject 6 in the 'body box' study. Here the afternoon study (●) shows a late rise in airways resistance (on the upper graph) with comparable change in lung volume (on the lower graph). No such change occurred in the morning study (○)

It could be argued that our failure to observe any airway response in all our subjects results from a large physiological variation in measurements of airway function which obscures any effect of smoking. It is unlikely that technical error contributed to this variation because of the precautions taken to increase precision and objectivity of measurement. An on-line mini-computer was used to analyse the flow and volume signals for the MEFV and PEFV studies. In order to remove observer bias the three observers who independently analysed the slopes of the transducer signals on the X-Y tracings in the body box study were unaware of the protocol and that comparisons between smoking and control studies was to be used to measure the effect of smoke inhalation.

Other sources of variation in the measurements were determined quantitatively by factorial analysis of variance. This provided a measure not only of the influence of major effects but also of their interactions. The remaining unattributable variation or technical error ('noise') was small, so that factors such as subjects, time of day and their interactions were highly significant and were quantitatively much greater than any effects of smoking.

It could be further argued that our smokers failed to inhale the cigarette smoke.

However, in the MEFV and PEFV studies the change in levels of venous blood nicotine was well in excess of that seen during purely 'mouth smoking' (Haines et al. 1974). In the body box study the smokers took a similar number of drags to the other studies.

It is possible that the smoke for the cigarettes we used was less irritant than that of earlier studies. Certainly they were filtered, being of a low tar and nicotine yield (1.01 mg of nicotine per cigarette) whereas in earlier studies plain high tar/nicotine cigarettes were used (Nadel & Comroe 1961; Clarke et al. 1970; Guyatt et al. 1970; Hamosh & Da Silva 1977). Whether these factors are important in determining the size of an airway response is uncertain. Some workers have shown no difference between the effects of high and low tar, filtered and unfiltered cigarettes (Nadel & Comroe 1961), whereas others have shown that filters reduce bronchoconstriction (Robertson et al. 1969; Clarke et al. 1970). There is obviously need for further study of this aspect of the problem.

When comparing the relative sensitivities of different measurements of airway function for detecting the acute response to cigarette smoke, it is difficult to arrive at firm conclusions when there appears to be such a small effect. We found that both the MEFV and PEFV detected the acute cigarette response in Subject 1 and that the $\dot{V}max_{50}$ and $\dot{V}max_{40}$ from these two manoeuvres were comparable as has been described by others (Hamosh & Da Silva 1977). The measurement of airways resistance (R_{aw}) which avoided a preceding full inhalation appeared to be no better in detecting the acute airway resonse.

The inhomogenity of response to tobacco smoke in our homogenous group of subjects suggests that there may be a subgroup of smokers who have enhanced susceptibility to inhaled smoke. An alternative explanation might be that responders smoke in a way which causes pharyngeal and laryngeal irritation, whereas non-responders avoid this effect. Airway narrowing could therefore be considered either protective and beneficial or a potentially harmful host response.

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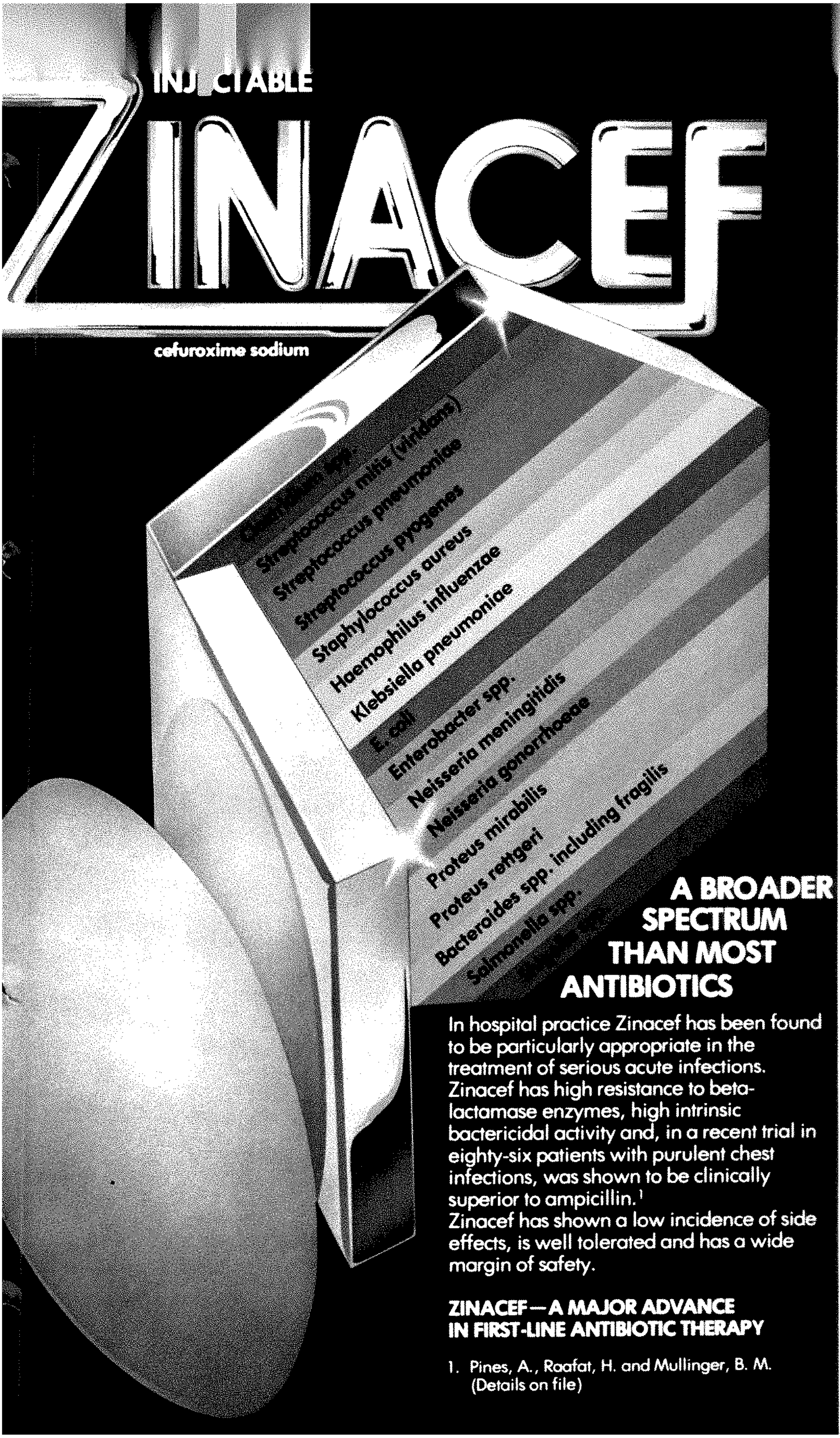

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- Bone and joint infections
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A COMPUTER SIMULATION OF PHYSIOLOGICAL FACTORS CONTRIBUTING TO HYPERVENTILATION AND BREATHLESSNESS IN CARDIAC PATIENTS

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Royal Postgraduate Medical School, London

Summary

A computer model of human respiration is of value for teaching the basic principles of respiratory physiology to students. An extension of this educational use is in the theoretical exploration of the relative importance of individual factors which may be contributing to disordered function in common clinical problems. For example, when a cardiac patient becomes breathless with increase in ventilation during exercise there are alterations in many physiological variables. The influence of their individual contributions on the total ventilation and thence possibly on breathlessness is often difficult to estimate. We present a theoretical analysis using MACPUF, a digital computer simulation of circulation and gas exchange which can be used to estimate the quantitative contribution of relevant physiological variables by altering them singly and in combination. Alterations in dead space, physiological shunt and pulmonary compliance individually produce only small increases in ventilation. Increased neurogenic drive (e.g. from lung reflexes triggered by pulmonary congestion) is a potentially important but very variable factor. A more important influence on ventilation appears when cardiac output is reduced and anaerobic metabolism simulated, causing changes in blood gas tensions and acidaemia which then change ventilation. Any increase in ventilation becomes more significant as a cause of breathlessness when ventilatory capacity is reduced, which in cardiac patients it not infrequently is.

INTRODUCTION

When considering factors that may be contributing to breathlessness it is useful to ask two questions. First, is the patient having to breathe excessively? and second, is his ability to meet the increased ventilatory demands impaired? The importance of the relationship between ventilatory demands and ventilatory capacity has been recognized for a long time (Peabody 1916; Knipping et al. 1931; Kaltreider & McCann 1937; Cournand & Richards 1941) and has been called the dyspnoeic index. It is axiomatic that anything which tends to raise this ratio, either by increasing ventilatory demands or by reducing the bellows capacity of the lungs, may be recognized as breathlessness. When a cardiac patient exercises this ratio may be disturbed in many ways (Fig. 1). Two important changes need consideration: first, the effects of a low cardiac output and second congestive changes in the lung (Bates et al. 1971; Cotes 1975). Failure of the cardiac output to increase normally on exercise causes inadequate blood supply to working muscle; consequent impairment of oxygen supply results in anaerobic glycolysis, producing lactic acid. This is to a large extent buffered by tissue bicarbonate with the release of equimolar amounts of carbon dioxide which has to be excreted in addition to that produced by aerobic metabolism; consequently if the arterial blood $P\mathrm{co}_2$ is not to rise there must be an increase in alveolar ventilation. Unbuffered hydrogen ions also can result in an additional ventilatory drive. In any patient whose exercise capacity has been restricted, lack of physical fitness may further increase the rise in blood lactate concentration (Saltin et al. 1968).

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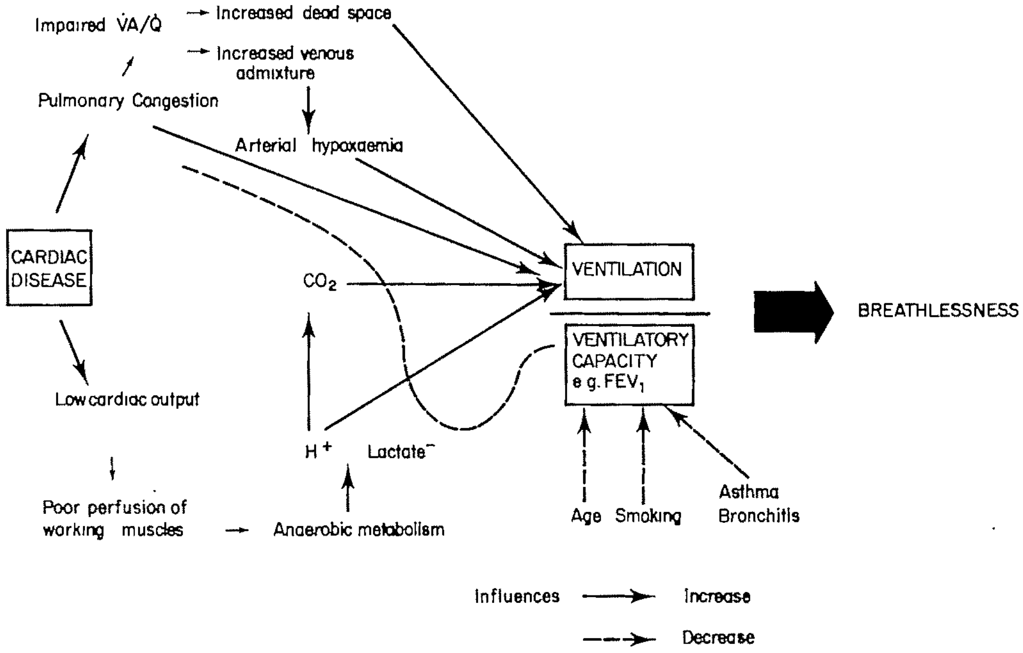

Fig. 1. Breathlessness is influenced by the relationship between ventilatory demand and ventilatory capacity, both of which can easily be measured. Cardiac disease (on the left) leads to dyspnoea by raising this ratio through many different physiological pathways. The effects on the systemic circulation and the lungs have both been represented; in addition to $\dot{V}A/\dot{Q}$ mismatch pulmonary congestion increases ventilation by neurogenic drive. The ventilatory capacity may also be reduced and independent factors which reduce the FEV_1 may become important when considered in this way

Cardiac disorders also cause pulmonary congestion which can cause breathlessness in ill-understood ways. Stretch receptors, irritant receptors and juxtacapillary (J) receptors are stimulated and give rise to afferent stimuli via the vagi to the respiratory reticular formation in the medulla (Paintal 1973; Widdicombe 1974). If blood flow is diverted to the upper lobes ventilation–perfusion relationships are disturbed (Dollery & West 1960), so increasing venous admixture and causing arterial blood hypoxaemia, a further drive to breathing. Ventilation–perfusion imbalance in effect increases physiological dead space which will increase the amount of 'wasted' ventilation. Arterial blood $P\text{CO}_2$ will rise unless there is a compensatory increase in alveolar ventilation. As a result of acute or chronic pulmonary congestion several changes in lung mechanics occur: static compliance and lung volumes are reduced and airway resistance increases, each reducing ventilatory capacity (Pepine & Wiener 1972). In Fig. 1 this has been represented as FEV_1 because it is easy to measure and because the sustained maximal breathing capacity can be derived from the FEV_1 (Freedman 1969). Other factors unrelated to cardiac disorders, such as age, smoking and lung disorders with airway obstruction, can reduce the ventilatory capacity in the cardiac patient.

For any individual patient it may be asked whether one of these factors is more important than the others as a cause of hyperventilation and hence of breathlessness. The aim of the present theoretical study was to isolate the variables in the computer models used and to see how changes in the magnitude of each one separately and combined influence ventilation. The assumptions and mathematical formulations built into MACPUF, a digital computer simulation of human gas exchange and circulation (Dickinson 1977), were used for this.

MACPUF

The use of models to study clinical and physiological problems is not new. Earlier models have, however, generally been confined to a single aspect of respiratory physiology, often described in great detail. Mathematical descriptions of the relationship between ventilation–perfusion matching and blood gas composition (West 1969) or the mechanical properties of the lungs and the resultant patterns of air-flow (Fry 1968) are two examples. MACPUF goes much further towards achieving a complete theoretical description than anything hitherto. Great emphasis is placed on relevance to clinical medicine so that the model is as realistic as possible; it can describe transient and fluctuating phenomena as well as steady states. The model was originally intended for teaching clinical respiratory physiology to medical students. It is easy to operate; no previous computer experience is needed.

The model embodies empirical relations such as the blood and tissue dissociation curves for respiratory gases, regressions describing ventilatory responses to CO_2, hypoxaemia and acidaemia and algebraic formulations governing cardiac output and gas exchange calculations. Ventilation–perfusion matching in the lung is based on the three compartment model (Riley & Cournand 1949); this assumes an 'ideal' gas-exchanging compartment, a compartment for right to left shunt (venous admixture) and a ventilatory compartment in which there is no blood flow, i.e. physiological dead space. The computational procedures have been justified by comparing the model's behaviour with physiological observations. A full description of the model, computer program facilities and instructions for use is available (Dickinson 1977).

USE OF MACPUF TO SIMULATE EXERCISE

Exercise is simulated in the model by increasing the function for metabolic rate. This results in a linear increase in alveolar ventilation as oxygen uptake increases; this is shown as the lowest plot in Fig. 2A. Since there is no generally agreed explanation for the normal increase of ventilation with exercise, the model has a built-in (by analogy 'learned') response which results in an alveolar ventilation sufficient to maintain stable blood oxygen and CO_2 tensions at all levels except the most strenuous. The sum of alveolar ventilation and dead space ventilation is total ventilation. Any increase in dead space necessitates an increase in total ventilation if the blood gas tensions are to remain stable. When increments of up to 400 ml of extra dead space are made the resulting effects on total ventilation are shown in Fig. 2A. These magnitudes were chosen because they give values for dead space/tidal volume ratio corresponding to those found in exercising patients after myocardial infarction (Higgs et al. 1968) and in those with mitral stenosis (Aström 1970). The effects on total ventilation of increases in dead space alone appear small.

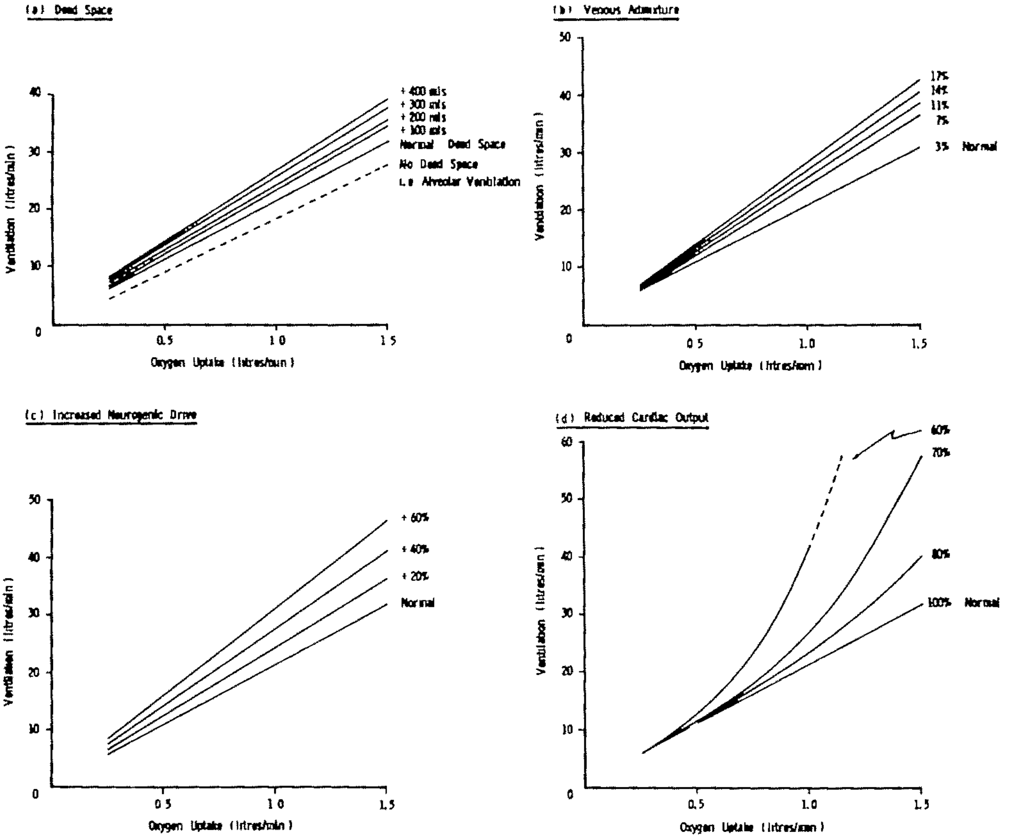

Fig. 2. The changes in total ventilation on exercise are calculated using MACPUF, a digital computer simulation of human gas exchange and circulation. Total ventilation is plotted against oxygen uptake. Shown are the effects on ventilation of separately altering (A) dead space; (B) venous admixture; (C) neurogenic drive; and (D) cardiac output

Blood flow through relatively underventilated areas of lung increases venous admixture. Fig. 2B shows the effect on total ventilation when venous admixture alone is increased; the changes are minor since the changes in arterial blood Po_2 calculated are small.

Pulmonary congestion stiffens the lungs (Pepine & Wiener 1972); this may have important effects on the pattern of breathing since if the lung becomes stiffer total ventilation is maintained by an increase in frequency of breathing at the expense of a fall in tidal volume (Hey et al. 1966). Lung elastance was increased from the normal value of 0.5 kPa/litre used in the model to 1 kPa/litre, corresponding with changes reported in chronic mitral stenosis (Wood et al. 1971) although in acute pulmonary oedema greater changes might be expected. In a normal subject exercising at an oxygen uptake of 1.5 litres/minute a small increase breathing frequency of 20% (3 breaths/minute) might be expected. Anxiety can result in more rapid breathing and this may contribute to the sensation of discomfort (Cotes et al. 1970).

The intrinsic neurogenic drive to breathing (i.e. the drive operating independently of chemical stimuli) can be increased by increased stimulation of receptors in the lung as a result of congestion and other conditions such as cardiac pain or anxiety. Though numbers can be given to these sensations it is possible to make the model hyperventilate and in Fig. 2C this has been done by increasing ventilation by up to 60% which at an oxygen uptake of 1.5 litres/minute, results in a fall of arterial Pco_2 to 3.8 kPa.

Reduced cardiac output limits oxygen supply to working muscle. Assuming no congestive changes in the lung in this experiment we are seeing the sole effect on ventilation of lactate production from anaerobic metabolism as it occurs during exercise (Fig. 2D). The chosen reductions in cardiac output to as low as 70% of normal correspond with values found in patients with cardiac disease (Gazetopoulos et al. 1966; Sannerstedt 1966; Higgs et al. 1968; Aström 1970; Sanne 1973). This simulation has produced larger changes in ventilation than any other factor studied in isolation; if cardiac output is reduced further to 60% then the simulated patient becomes incapable of exercise requiring an oxygen uptake of 1.5 litres/minute. The acid–base changes in the blood as lactate is generated from anaerobic metabolism are shown in greater detail in Fig. 3. In

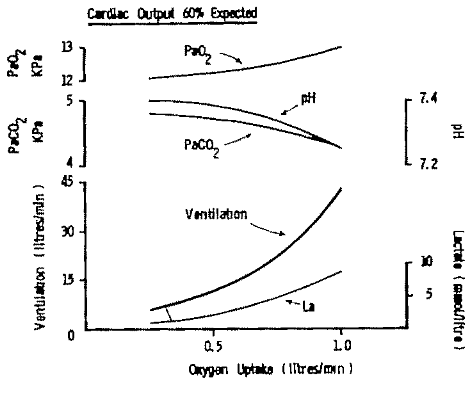

Fig. 3. The changes in blood gas tensions, pH and ventilation when a simulated patient (cardiac output 60%) exercises. Tissue oxygenation is inadequate, resulting in anaerobic metabolism. The rising concentration of lactic acid in the blood causes a fall in arterial blood pH and alveolar hyperventilation so that $Paco_2$ falls

this experiment a patient with a cardiac output of 60% of normal is exercising (no other factors have been altered). Lactate concentration rises to reach a level of 8.5 mmol/litre eight minutes after the start of exercise. This is partly buffered, creating CO_2 load to be excreted and a fall in arterial blood pH. These stimuli drive ventilation and as a result arterial blood $P\text{co}_2$ falls. This takes place in the absence of any arterial blood hypoxaemia (in fact arterial blood $P\text{o}_2$ is seen to increase).

The factors increasing ventilatory demands have so far been considered in isolation but in Fig. 4 they are combined. Ventilation–perfusion mismatch is represented by the addition of 100 ml of extra dead space with a 7% venous admixture; although their individual effects were slight their combined effect increased ventilation by 5 litres/minute (16%) at an oxygen uptake of 1.5 litres/minute. Neurogenic drive is increased by 20% (this might be a reasonable representation of the ventilatory effects of pulmonary congestion) and, to complete the picture, cardiac output is now reduced to 80%. When small changes in factors which individually have minor effects are added together the combination increases total ventilation at an oxygen uptake of 1.5 litres/minute by as much as 50% of the control value (16 litres/minute). The individual changes made are realistic, as is the resulting change in ventilation when they are combined (Gazetopoulos et al. 1966; Sannerstedt 1966; Aström 1970; Sanne 1973).

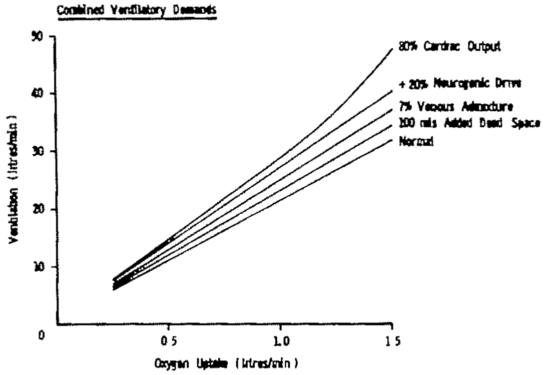

Fig. 4. Simulation using MACPUF of the combined ventilatory demands of an exercising cardiac patient. Factors which individually produce a small increase in ventilation summate to produce an appreciable increase in ventilation

These combined drives to ventilation become even more potent as a cause of breathlessness when they are considered in relation to the ventilatory capacity. As the lungs become congested the lungs become stiff and so increase the work of breathing, as well as reducing ventilatory capacity. The combined effect on the simulated patient of increased ventilatory demands and a reduced ventilatory capacity is shown in Fig. 5 in which the ventilation (expressed as a percentage of the ventilatory capacity) is plotted against oxygen uptake. The lowest line represents the normal subject. The next line is that of the cardiac patient with the full simulation of extra ventilatory demands shown in Fig. 4, but with a normal ventilatory capacity (100%). Maintaining the added ventilatory demands unchanged, further decrements in the ventilatory capacity by definition

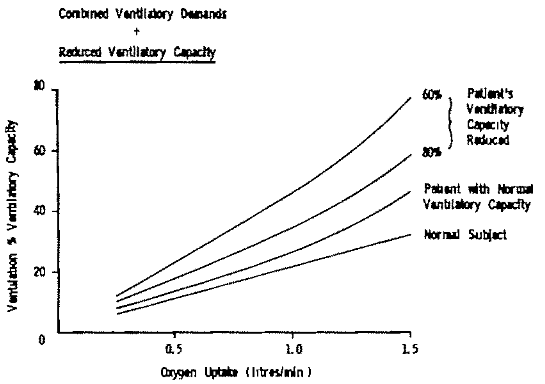

Fig. 5. Ventilation, as a percentage of ventilatory capacity (i.e. the dyspnoeic index), increases on exercise. The combined ventilatory demands of the simulated cardiac patient when related to the reduction in the ventilatory capacity indicate the level of exercise at which breathlessness is likely to occur.

increase the dyspnoeic index. The level of exercise at which breathlessness is likely to occur is thus reduced.

DISCUSSION

The breathlessness of cardiac patients is often poorly understood because of the complexity and interrelationships of the factors involved. When investigating these patients it is common to detect a variety of changes but difficult to determine the magnitude of the contribution of each to the ventilation response to exercise. In this simulation we have given the individual factors magnitudes so that the magnitudes of their individual and combined effects can be estimated. Isolated increases in dead space and venous admixture appear to produce only small changes, but if ventilation–perfusion mismatch resulting from pulmonary congestion is present then, using the individual values instanced above, their effects combined produced an increase in total ventilation of approximately 16%. The change in tidal volume that would result (10%—2 litres to 2.2 litres) would probably be too small for the patient to detect (West et al. 1975).

Congestion of the lungs initiates reflexes causing an increase in neurogenic drive to breathing, which may be further augmented by hyperventilation due to anxiety. Likely to be linked with this is a change in breathing pattern to higher frequency and lower tidal volume (Hey et al. 1966) resulting from pulmonary congestion. This can increase dead space ventilation as a proportion of total ventilation and create a sensation of discomfort (Cotes et al. 1970). The results for the simulated patient (Fig. 4) correspond with observed value for ventilation in exercising cardiac patients studied in a laboratory. Since the alterations in the other factors are representative, the contribution allotted to a neurogenic factor would appear to match what might happen in life. The largest increase in ventilation would appear to occur when a cardiac output results in poor perfusion of working muscle and increased anaerobic metabolism. The combined effects of increased dead space, increased venous admixture and increased neurogenic drive (to represent pulmonary congestion) equivalent to that produced by reducing cardiac output to 80% of the normal expected output for the level of exercise studied; this tends to confirm earlier work (Gazetopoulos et al. 1966; Sanne 1973), indicating that pulmonary congestion is also an important cause of hyperventilation.

Initially we considered factors which separately cause hyperventilation. Then the computer model combined them in a way which, of course, depended on the way the program has been written. It is well known that some physiological mechanisms interact arithmetically whereas among others there is potentiation. If there were reason to believe that in cardiac disorders there was a particular type of interaction, MACPUF could probably be modified to explore this further. So far we have considered only factors which cause hyperventilation. The relationship of ventilation to ventilatory capacity influences the sensation of breathlessness. Pulmonary congestion reduces ventilatory capacity, so the chance that breathlessness will develop is increased. Sensory perceptions are too complex to formulate with this computer simulation, but when simultaneous changes in ventilatory demands and ventilatory capacity are taking place (Fig. 5), the effect on the dyspnoeic index is clearly synergistic.

This study offers a hypothetical approach, based on conventional concepts, to estimate how several factors, which individually may have only a slight effect, can act in combination as a potent source of breathlessness. The practical investigation of cardiac patients complaining of breathlessness of course begins with consideration of the simple relationship between ventilatory demands and ventilatory capacity.

ACKNOWLEDGEMENTS

We should like to thank Professor C. J. Dickinson who wrote the programme for MACPUF and made the model available for this study for close cooperation and helpful advice. We also thank Professor E. J. M. Campbell for valuable discussions.

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IMPAIRED POLYMORPHONUCLEAR LEUCOCYTE CHEMOTAXIS AFTER INFLUENZA VIRUS INFECTION

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Summary

Polymorphonuclear leucocyte function was assessed in 13 patients with influenza by measuring phagocytosis of staphylococci and chemotaxis. Significant impairment of chemotaxis was shown. Subsequently polymorph chemotaxis was found to be impaired in a group of volunteers infected with virus recombinants of A/New Jersey/8/76 but not in volunteers infected with a virus recombinant of A/Victoria/3/75. These results accord well with the in vitro effects of certain influenza viruses on polymorph function and suggest that interference with polymorph function may predispose to bacterial pneumonia after clinical influenza.

INTRODUCTION

Bacterial pneumonia complicates human influenza. It is thought that this is usually a result of local virus-induced damage within the respiratory tract (Loosli 1973). Lesions in tracheal and bronchial epithelium have been described in both fatal (Mulder & Hers 1972) and non-fatal (Walsh et al. 1961) cases. These lesions are probably responsible for the impaired clearance of 99 technetium-labelled Teflon particles from the airway (Camner et al. 1973). We and others have studied the effects of influenza virus on human polymorphonuclear leucocytes in vitro (Larson & Blades 1976; Larson et al. 1977; Ruutu et al. 1977) and have suggested that virus impairment of polymorph function also may play a role in the development of bacterial pneumonia. Certain A and B strains can impair polymorph chemotaxis and abnormalities of phagocytosis and of random migration are seen as well. The effects on polymorphs are caused by purified virus suspensions, do not require fully infective virions and can be produced at low virus particle/cell ratios. We therefore thought that such changes might be found in cells in the circulation of patients with the disease. This report describes the measurement of polymorph function in human subjects experiencing influenza virus infection.

Materials and Methods

Tests of phagocytosis and chemotaxis were performed on 10 ml of heparinized venous blood sedimented with 6% dextran 70 using methods described previously (Larson et al. 1977). Phagocytosis results are expressed as the percentage of 200 enumerated cells with cocci present. Chemotaxis results are expressed either as the average number of migrating cells of five counted fields in each of two or three replicate filters, or as the percentage of a simultaneously tested normal control. Tests of chemotaxis in Common Cold Unit (CCU) volunteers used polymorphs suspended at 5×10^6/ml while in other studies the concentration was 1×10^6/ml. This accounts for the higher numbers of migrating cells seen in Fig. 4.

Virus isolation was performed in tissue culture or in embryonated eggs. Haemagglutination-inhibiting (HAI) and complement-fixing (CF) antibody titres were determined simultaneously on paired serum specimens using standard methods.

Thirteen patients were studied; their clinical and virologic findings are summarized in Table I. Studies of polymorph function were performed within three days of admission in all except Case 7; the time of admission to hospital, however, ranged from one day to two weeks after the onset of symptoms. All patients except Cases 4, 9 and 13 received antibiotics, six receiving ampicillin, penicillin and/or flucloxacillin, three co-trimoxazole and one erythromycin. Only in Case 7 did such treatment achieve prompt resolution of fever and clearing of the pulmonary infiltrate; the polymorph studies were performed after resolution of the pneumonia in this case.

Table I. Clinical findings and virology in 13 patients with influenza virus infection

Case No.	*Chest X-ray*	*Sputum bacteriology*	*Days febrile*	*Virology*
1*	Clear	Normal flora	5	16-fold HAI rise to A/Victoria
2	Bilateral pneumonia	*S. aureus* *Str. pyogenes* group A	13	Influenza B CF > 1:640
3	Clear	Normal flora *Haemophilus* sp.	14	A/Victoria isolated
4	Clear	Not done	4	A/Victoria isolated
5	Pneumonia, pleurisy	Normal flora	4	A/Victoria isolated
6	Clear	Not done	2	A/Victoria isolated
7	Pneumonia	*Str. pneumoniae*	1	Influenza A CF 1:640
8	Pneumonia	Normal flora	15	4-fold HAI rise to A/Victoria
9	Not done	Not done	2	16-fold HAI rise to A/Victoria
10	Not done	Normal flora	3	A/Victoria isolated
11	Clear	Normal flora	15	A/Victoria isolated
12	Clear	*Haemophilus* sp.	9	4-fold HAI rise to A/Victoria
13	Bilateral pneumonia	Normal flora	4	8-fold CF rise to Influenza A

* Patients are ranked 1 (low) to 13 (high) in order of chemotaxis results (see Fig. 2).

Eight of these patients had tests of phagocytosis and nine had tests of chemotaxis five to six months after recovery from their illness. All were then well except one woman with recurrent asthma and impaired pulmonary function.

Control subjects were four healthy young adults, one of whom was tested simultaneously with each patient. For purposes of calculation control values were not duplicated in cases where more than one patient was studied in a test; this gives fewer values for controls than for patients in Figs 1 and 2.

Volunteers at the Common Cold Unit in Salisbury received one of three recombinants of A/New Jersey/8/76 (HSw$_1$N$_1$) in studies conducted by Dr A. S. Beare. Two recombinants were A/PR8/34-NJ/8/76 and one was A/Okuda/57-NJ/8/76. Polymorph chemotaxis was measured on the day of inoculation or the day before and two or three days after inoculation. Virus isolation or antibody rise showed that 12 subjects were infected and their results have been combined.

Volunteers at the Clinical Research Centre in Harrow were given a live recombinant influenza virus (A/PR8/34-Victoria/3/75) as nasal drops in a trial of candidate vaccine strains conducted by Dr K. G. Nicholson. Polymorph studies were done three days before or on the day of inoculation and two, three or four days after. Ten volunteers were infected and only their results have been analysed.

Clinical reactions were scored according to standard procedure at the CCU by an independent observer and at Harrow by the volunteers themselves on a record card. Reactions graded mild are those with significant upper respiratory symptoms alone while those graded moderate had constitutional upset in addition.

RESULTS

The results of test of the capacity of polymorphs from influenza patients to phagocytose staphylococci are shown in Fig. 1. The patient mean of 68 is not significantly different from the control mean of 73. When expressed as a percentage of the control values, polymorphs from acutely ill patients averaged 93% while those from convalescent patients averaged 94% (data not shown). Because this test failed to demonstrate any significant functional impairment, it was not included in the subsequent studies on volunteers.

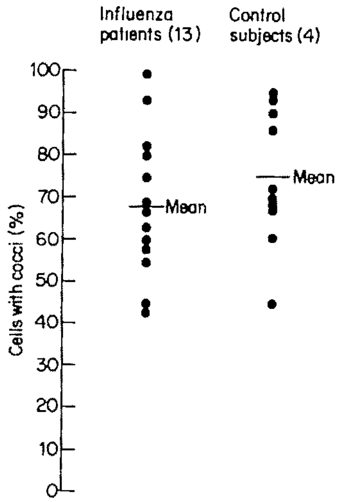

Fig. 1. Polymorph phagocytosis in influenza patients and control subjects

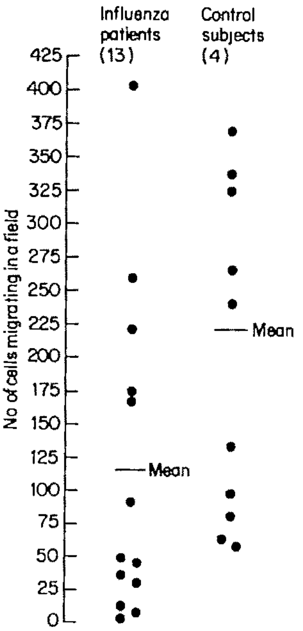

Fig. 2. Polymorph chemotaxis in influenza patients and control subjects

The chemotaxis results from patients are shown in Fig. 2. Seven patients had values below the lowest control value and the patient average is significantly lower than the control average ($P < 0.05$, two-sample unpaired *t*-test, $P \simeq 0.06$ by the non-parametric Wilcoxon rank sum test). Table I ranks patients by the results of polymorph chemotaxis tests. Patients with pneumonia and patients with a prolonged febrile course are distributed throughout the entire range of chemotaxis values. Cases 2 and 7 shown to have bacterial pathogens in their sputum had very low chemotaxis, however.

Fig. 3 compares chemotaxis in patients when acutely ill with that after convalescence. Lines connect the results of studies on the same patient. Seven of the nine patients studied showed marked rises in chemotaxis, expressed as a percentage of the control. Of the four patients not studied in convalescence, two had very low acute values and two moderately high. The difference between acute and convalescent averages is significant whether these four are included in the calculation ($P < 0.02$, two-sample unpaired t-test) or excluded ($P < 0.01$, paired t-test).

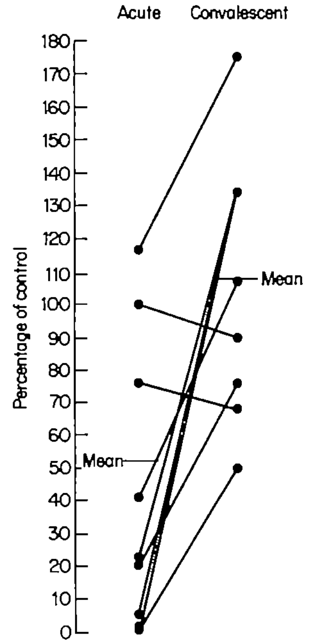

Fig. 3. Polymorph chemotaxis in acute and convalescent influenza patients. Lines connect determinations on a single patient

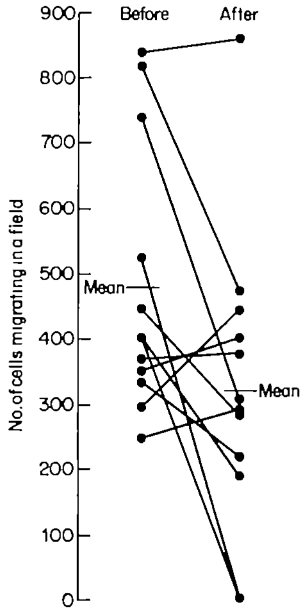

Fig. 4. Polymorph chemotaxis in volunteers before and after inoculation with influenza virus recombinants A/PR8/34, A/Okuda/57-NJ/8/76 (HSw_1N_1). Lines connect determinations on a single subject

These findings encouraged us to examine polymorph chemotaxis in clinically milder influenza virus infections under conditions where measurements could be made prospectively. Fig. 4 illustrates the results of the first such study. Seven volunteers showed a decrease in chemotaxis, four showed no change and one might be said to have had a rise. The decreases in four subjects were very marked. The averages before and after inoculation are significantly different ($P < 0.05$, paired t-test). The three virus strains inoculated differed from one another in their ability to induce infection and to cause clinical reactions. Six of the volunteers had mild to moderate clinical reactions, but decreases in chemotaxis were not exclusively associated either with a particular strain or with clinical reactions. The numbers receiving each virus strain were too small to show a significant relation between either virus strain or clinical reaction and chemotaxis.

Fig. 5 summarizes the results of a further study of chemotaxis after inoculation with a different recombinant virus. It caused definite clinical reactions in eight of the ten subjects. Average values for chemotaxis were not significantly different before and after inoculation and the figure suggests no general trend.

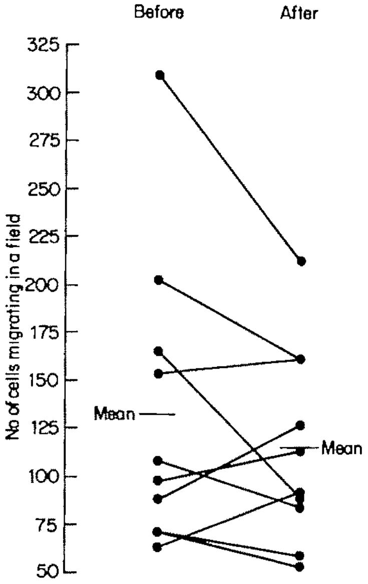

Fig. 5. Polymorph chemotaxis in volunteers before and after inoculation with influenza virus recombinant A/PR8/34-Victoria/3/75. Lines connect determinations on a single subject

DISCUSSION

These results indicate that infection with certain influenza viruses is associated with impaired polymorph chemotaxis. The agreement between the findings in patients and in volunteers and those we reported earlier in in vitro studies suggests that the impairment is a direct effect of the virus particle. Polymorphs treated with diluted virus suspensions or with purified virus in vitro are chemotactically inhibited while those treated with infected allantoic fluid with most of the virus removed by filtration are not inhibited. Inhibition of chemotaxis in vivo might be due to fever or to hypoxaemia and only indirectly related to the virus. However, this is unlikely to be the case in volunteers who experience only mild clinical illness. We looked for circulating inhibitors of chemotaxis by mixing acute serum from two patients with impaired chemotaxis with polymorphs from a normal donor; no impairment of the normal cells was demonstrated (unpublished results).

Since the polymorphs we tested were obtained from peripheral blood, where does the virus–cell interaction occur? Infective virus is uncommonly detected in peripheral blood even in clinically severe influenza and exposure to the virus may occur when the polymorphs traverse the pulmonary circulation. The clinical result of impaired polymorph function is likely to be most apparent in the respiratory tract where polymorphs have the greatest exposure to virus and where there will be additive effects from damaged mucous membrane, loss of ciliated cells and perhaps impaired macrophage function (Kleinerman et al. 1975).

Not every infected subject had impaired chemotaxis and indeed the results in Fig. 2 suggest that much of the observed effect derives from a few who have severely depressed responses. It is not clear whether this is owing to differences in the degree of a host response or in the timing of the test. We have done serial studies in only three patients and some variation in the degree of chemotactic inhibition was observed. A further test of our hypothesis will be to see whether those with impaired chemotaxis are actually the ones who demonstrate significant bacterial infection. We had only two cases in which bacterial pathogens were isolated from the sputum; the remainder probably had virus pneumonia. Further studies to establish this correlation are necessary.

The negative findings after infection with the A/PR8/34-Victoria/3/75 recombinant suggests that not every infection shows reduced polymorph function. In vitro we have been unable to show effects on chemotaxis with viruses A/PR8/34, NWS and one of the A/New Jersey/8/76 recombinants inoculated in the experiment shown in Fig. 4. Ruutu et al. (1977) found no effect with a strain of B/Finland/1/69, although agglutination of the polymorphs occurred at high virus concentrations, a phenomenon we have also observed. On the other hand, A/Victoria and all of the other recombinants (Figs 4 and 5) tested here did impair chemotaxis in vitro. The correlation between in vitro and in vivo behaviour is likely to be complex and many components of virus behaviour like replication, attachment and neuraminidase activity may prove to be important.

Phagocytosis was not affected in our studies. Ruutu and Kosunen (1971) used similar methods to study phagocytosis in patients infected with A2/Hong Kong viruses and also found no change during the acute illness. Phagocytosis two weeks later was enhanced, but after four months had declined back to acute levels. Our results are thus consistent with their findings. These methods have been criticized as being primarily a measure of phagocytic capacity (Michell et al. 1969) and it is possible that kinetic studies using phagocytosis saturating concentrations of staphylococci might show a defect.

ACKNOWLEDGEMENTS

We acknowledge the help of Dr A. S. Beare and Dr K. G. Nicholson who allowed us to study volunteers under their supervision, Dr J. W. Craig for clinical assessment of volunteers, Mr D. G. Altman for statistical advice and Mr J. V. Parry for technical assistance.

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INHALED Ventolin

(salbutamol BP)

bronchodilator therapy no asthmatic need be without

Primary therapy
in reversible airways obstruction

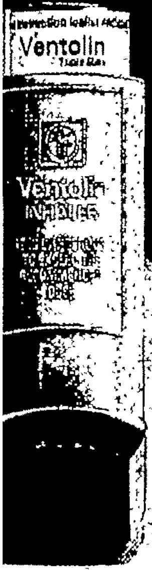
Proven efficacy and β_2-selectivity

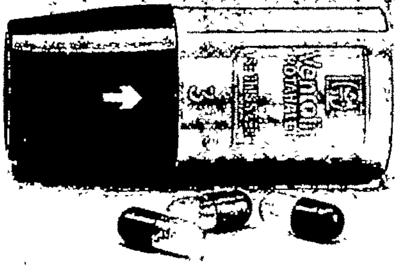
Long acting
yet with a rapid onset of action

Protects against exercise induced asthma

Microgram dosage
avoids systemic side effects

Available as metered-dose aerosol
and Rotacaps with Rotahaler





Cross-section of bronchiole
illustrating bronchospasm
due to contraction of
respiratory smooth muscle.

> “Why are so many asthma patients treated with oral drugs when their symptoms could be more effectively controlled, and with much less risk, by therapy administered by inhalation? ... All patients with asthma should be treated with a bronchodilator aerosol, and it is rational to use only the more selective sympathomimetic drugs...”

(*Modern Medicine*, May, 1977, p. 57-58)

INHALED VENTOLIN

INHALED BECOTIDE

PATIENT INSTRUCTION

It is important to ensure that patients receiving inhalation therapy are correctly instructed in the use of the device being prescribed. For this purpose demonstration units are available on request from Allen & Hanburys Ltd. The patient's acquired technique should be monitored by re-checking at suitable intervals. Generally speaking, patients unable to use pressurised aerosols efficiently can be satisfactorily treated using the alternative Rotacap/Rotahaler system which, for them, provides a greater degree of certainty and a better guarantee of effectiveness. Any initial problems with the manipulation of the Rotahaler are usually overcome as the patient becomes more familiar with its use. In the case of young children and patients with arthritis of the hands it may be preferable for the device to be loaded by the parent or other person. When Ventolin Rotacaps are being used for the relief of acute bronchospasm it may be convenient to load a Rotacap into the device so that the dose is readily available. Ventolin and Becotide Rotahalers are supplied in plastic boxes for carrying in the pocket or handbag. The daily requirement of Rotacaps may be inserted into the spaces provided in the box to encourage compliance. A replacement Ventolin or Becotide Rotahaler should be prescribed at approximately six-monthly intervals.

RODUCT INFORMATION

ESENTATION AND BASIC NHS COST

ntolin Inhaler is a metered-dose aerosol delivering 100mcg salbutamol BP per actuation. ch canister contains 200 inhalations Basic NHS cost £1.96.

ntolin Rotacaps 200mcg & 400mcg each contain a mixture of the stated amount of icrofine salbutamol BP (as sulphate), and larger particle lactose in light blue/colourless or rk blue/colourless hard gelatine cartridges, respectively Containers of 100. Basic NHS st £2 96 and £4.00, respectively

ntolin Rotahaler for use in conjunction with Ventolin Rotacaps. Basic NHS cost 65p.

DICATIONS

utine control of bronchospasm in bronchial asthma, bronchitis and emphysema, or as quired to relieve attacks of acute bronchospasm. Doses may also be taken before exertion prevent exercise induced asthma or before exposure to a known unavoidable challenge.

SAGE AND ADMINISTRATION

single doses for the relief of acute bronchospasm, for managing intermittent episodes asthma and to prevent exercise-induced bronchospasm.

ing Ventolin Inhaler – *Adults:* one or two inhalations.

ildren: one inhalation increasing to two if necessary.

ing Ventolin Rotahaler – *Adults:* one Ventolin Rotacap 200mcg or 400mcg.

ildren: one Ventolin Rotacap 200mcg

r chronic maintenance or prophylactic therapy

ing Ventolin Inhaler – *Adults:* one or two inhalations three or four times a day

ildren: one inhalation three or four times a day increasing to two inhalations if necessary.

ing Ventolin Rotahaler – *Adults* one Ventolin Rotacap 400mcg three or four es a day.

ildren: one Ventolin Rotacap 200mcg three or four times a day.

r optimum results in most patients inhaled Ventolin should be administered regularly.

NTRA-INDICATIONS

ntolin preparations should not be used for the prevention of threatened abortion.

ECAUTIONS

previously effective dose of inhaled Ventolin fails to give relief lasting at least 3 hours, e patient should be advised to seek medical advice. Ventolin should be administered utiously to patients suffering from thyrotoxicosis Unnecessary administration of drugs ring the first trimester of pregnancy is undesirable

DE EFFECTS

important side effects have been reported following treatment with inhaled Ventolin.

ODUCT LICENCE NUMBERS

ntolin Inhaler 0045/5022; Ventolin Rotacaps 200mcg 0045/0116;
ntolin Rotacaps 400mcg 0045/0117.

PRODUCT INFORMATION

PRESENTATION AND BASIC NHS COST

Becotide Inhaler is a metered-dose aerosol delivering 50mcg beclomethasone dipropionat BP per actuation. Each canister contains 200 inhalations. Basic NHS cost £3.84.

Becotide Rotacaps 100mcg & 200mcg each contain a mixture of the stated amount of microfine beclomethasone dipropionate BP and larger particle lactose in buff or chocolate brown/colourless hard gelatine cartridges, respectively Containers of 100. Basic NHS cost £5.84 & £7.78, respectively.

Becotide Rotahaler, for use in conjunction with Becotide Rotacaps Basic NHS cost 65p.

INDICATIONS

Bronchial asthma especially in patients whose asthma is not adequately controlled by bronchodilators and patients with severe asthma who would otherwise be dependent on systemic corticosteroids or adreno-corticotrophic hormone (ACTH) or its synthetic equivalent.

DOSAGE AND ADMINISTRATION

Using Becotide Inhaler – *Adults:* two inhalations three or four times a day is the usual maintenance dose. In severe cases dosage may be started at twelve to sixteen inhalations per day and subsequently reduced when the patient begins to respond.

Children: one or two inhalations, two, three or four times a day according to the response.

Using Becotide Rotahaler – *Adults:* one 200mcg Becotide Rotacap three or four times a day is the usual maintenance dose.

Children: one 100mcg Becotide Rotacap, two, three or four times a day according to the response

For optimum results inhaled Becotide should be administered regularly.

CONTRA-INDICATIONS

No specific contra-indications to inhaled Becotide are known but special care is necessary in patients with active or quiescent pulmonary tuberculosis

PRECAUTIONS

The maximum daily intake of beclomethasone dipropionate BP should not exceed 1mg. Inadequate response after the first week of inhaled Becotide therapy suggests that excessive mucus is preventing penetration of inhaled drug to the target area. A short course of systemic steroid in relatively high dosage should be given and therapy with inhaled Becotide continued.

Unnecessary administration of drugs during the first trimester of pregnancy is undesirable.

When transferring patients to Becotide from systemic steroid therapy the possibility of adrenocortical suppression should be considered and patients given a supply of oral steroids for use during periods of stress Please refer to the detailed procedure described in the data sheets for Becotide Inhaler and Becotide Rotacaps.

SIDE EFFECTS

Occasional candidiasis of the mouth and throat (thrush) occurs in some patients, particularly those with high blood levels of Candida precipitins Topical therapy with antifungal agents usually clears the condition without withdrawal of Becotide.

PRODUCT LICENCE NUMBERS

Becotide Inhaler 0045/0089; Becotide Rotacaps 100mcg 0045/0119;
Becotide Rotacaps 200mcg 0045/0120

INHALED Ventolin and Becotide

A rational basis for prescribing in asthma

Full prescribing information is available on request
Ventolin, Becotide, Rotacap, Rotahaler, are trade marks of ALLEN & HANBURYS LTD., London E2 6LA

INHALED

Becotide

(beclomethasone dipropionate BP)

for the asthmatic who needs more than a bronchodilator

Controls the inflammatory processes in more severe asthma

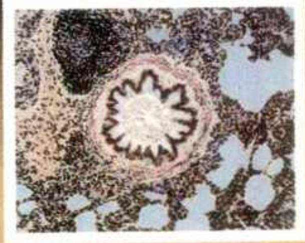
Restores the response to bronchodilators

Avoids the side effects associated with systemic steroids

Eliminates or greatly reduces the need for systemic steroids in steroid-dependent patients

Obviates physical disfigurement and stunting of growth in children

Available as metered-dose aerosol and Rotacaps with Rotahaler



Cross-section of bronchiole illustrating bronchospasm complicated by bronchial mucosal oedema and hypersecretion of mucus.

> “To support this claim of extraordinary activity (of Becotide), there are not only statistically valid comparisons but also numerous validated individual experiences. These include the impressive therapeutic results in patients with severe asthma not controllable with high daily doses of systemic steroids; the beneficial responses of those refractory to adrenergic agonists and unable to tolerate even suboptimal doses of theophylline; the suppression of asthma unresponsive to mediator-release inhibitors, such as cromolyn sodium; and, importantly, the high level of acceptance and compliance among people who do not comply with other standard therapeutic routines.”
>
> (*Lancet*, 1979, **i**, 932-933)

When the bronchodilator alone s inadequate, what next?

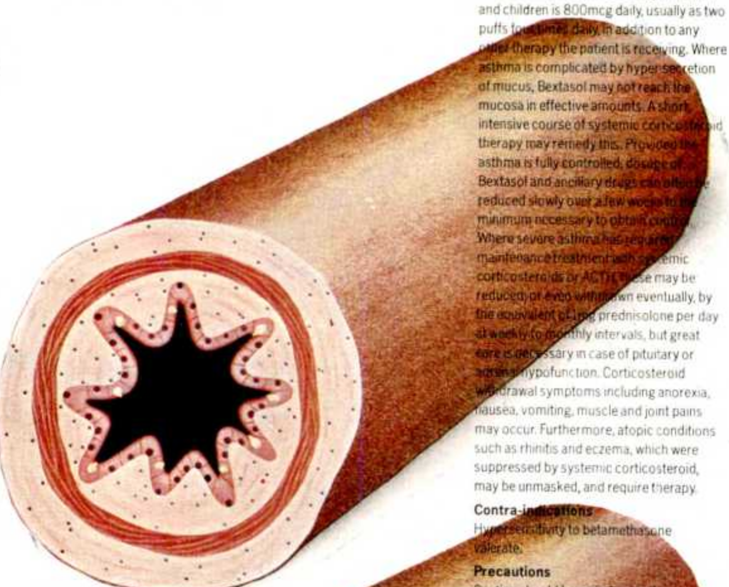
In controlling chronic asthma, the bronchodilator is usually the first line of attack. Often it will be the only treatment required.

In many cases, however, bronchodilators need to be given continuously and even then a number of patients will not be controlled satisfactorily—probably because the asthma is complicated by inflammation which bronchodilators will not control.

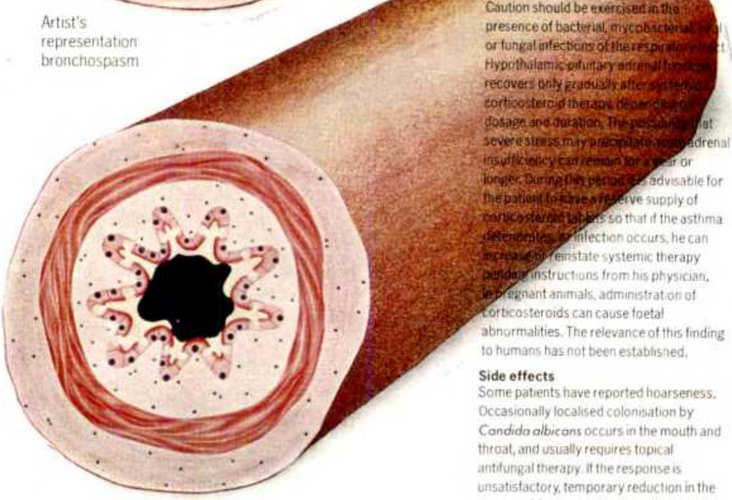
So when a second line of attack is required, Bextasol effectively controls the inflammatory process within the lungs and provides ideal prophylaxis of both intrinsic and extrinsic asthma. It offers steroid control without systemic side effects and usually produces a significant improvement in lung function.

In addition, no adverse effects on lung tissue have been reported after five years' clinical experience of inhaled steroid therapy.

In short, Bextasol inhaler allows the asthmatic to breathe and to live life to the full.



Artist's representation bronchospasm



Bronchospasm complicated by mucosal oedema and hypersecretion of mucus.

the clear decision

BEXTASOL

betamethasone valerate)

Prescribing information

Presentation
A pressurised aerosol containing a suspension of betamethasone valerate BP with propellants which supplies 200 metered inhalations, each provicing 100mcg of betamethasone valerate.

Dosage and administration
The recommended initial dosage in adults and children is 800mcg daily, usually as two puffs four times daily, in addition to any other therapy the patient is receiving. Where asthma is complicated by hypersecretion of mucus, Bextasol may not reach the mucosa in effective amounts. A short intensive course of systemic corticosteroid therapy may remedy this. Provided the asthma is fully controlled, dosage of Bextasol and ancillary drugs can often be reduced slowly over a few weeks to the minimum necessary to obtain control. Where severe asthma has required maintenance treatment with systemic corticosteroids or ACTH these may be reduced, or even withdrawn eventually, by the equivalent of 1mg prednisolone per day at weekly to monthly intervals, but great care is necessary in case of pituitary or adrenal hypofunction. Corticosteroid withdrawal symptoms including anorexia, nausea, vomiting, muscle and joint pains may occur. Furthermore, atopic conditions such as rhinitis and eczema, which were suppressed by systemic corticosteroid, may be unmasked, and require therapy.

Contra-indications
Hypersensitivity to betamethasone valerate.

Precautions
Caution should be exercised in the presence of bacterial, mycobacterial, viral or fungal infections of the respiratory tract. Hypothalamic-pituitary adrenal function recovers only gradually after systemic corticosteroid therapy, depending on dosage and duration. The possibility that severe stress may precipitate acute adrenal insufficiency can remain for a year or longer. During this period it is advisable for the patient to have a reserve supply of corticosteroid tablets so that if the asthma deteriorates, or infection occurs, he can increase or reinstate systemic therapy pending instructions from his physician. In pregnant animals, administration of corticosteroids can cause foetal abnormalities. The relevance of this finding to humans has not been established.

Side effects
Some patients have reported hoarseness. Occasionally localised colonisation by *Candida albicans* occurs in the mouth and throat, and usually requires topical antifungal therapy. If the response is unsatisfactory, temporary reduction in the dosage of Bextasol often speeds resolution.

See Data Sheet for complete information.

Product Licence number: 4/0142

Basic NHS cost (exclusive of VAT): £3·84 per inhaler.

Glaxo

Bextasol is a trade mark of
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Greenford, Middlesex UB6 OHE

Br. J. Dis. Chest (1980) *74*, 63

ETHNIC DIFFERENCES IN THE CLINICAL FEATURES OF SARCOIDOSIS IN SOUTH-EAST LONDON

DAVID HONEYBOURNE

King's College Hospital, London

Summary

The records of 91 patients who conformed to rigid criteria for the diagnosis of sarcoidosis were studied. These included 36 patients of West Indian and 47 of Caucasian origin. Comparison of these two groups showed a significantly later age of onset in the West Indians, who were also more liable to present with respiratory symptoms, particularly chest discomfort, to have eye involvement and palpable lymphadenopathy and to have a more disseminated disease than the Caucasian group. However, Caucasians were far more likely to have erythema nodosum. There was a tendency for the onset of symptoms in the whole group to occur between November to February.

Differences in sarcoidosis between ethnic groups within the same geographical area suggest variable host responses which may be dependant on their immunological response. The later age of onset of sarcoidosis seen in the West Indians might be explained by their later exposure to an invironmental transmissible agent.

INTRODUCTION

Sarcoidosis was probably first described by Hutchinson in 1877 who wrote about a case which would fit with skin sarcoidosis (Scadding 1967); the patient subsequently died of renal failure at King's College Hospital, London. Over a hundred years later we are still unsure of the aetiology of the disease. Transmissible agents have been suggested as a cause (Mitchell & Rees 1976), and the immunological manifestations of the disease have been widely investigated (James et al. 1975). Epidemiological studies may contribute clues to the aetiology and the present study was undertaken to look for differences in clinical features between West Indians and Caucasians. The present catchment area of King's College Hospital is similar to that of the 1950s, during which period Smellie and Hoyle (1960) collected important data. However, with the arrival of many immigrants to this area in the past 20 years a study of more recent trends in sarcoidosis is of interest.

Methods

A study was undertaken of the available case notes of patients with the diagnosis of 'sarcoidosis' made between 1960 and 1977. As far as possible the following information was obtained from the hospital records: criteria for the diagnosis, age of the patient at the onset of the symptoms which were thought by the clinician to be due to sarcoidosis, sex, ethnic origin, month of onset of symptoms, presenting symptoms, organs involved clinically and radiographically at the presentation and during later stages of the disease and use of corticosteroids in treatment.

In this study a diagnosis of sarcoidosis was accepted in patients having a positive Kveim test and/or other histology, or in patients who presented with an acute onset of erythema nodosum and bilateral hilar node enlargement and low tuberculin sensitivity. The data were analysed only after collection had been completed to avoid any observer bias and the results were analysed with Student's *t*-test and the χ^2 test (including Yates' correction factor as recommended by Armitage (1974)).

RESULTS

Information was obtained from all available case records of 99 patients. Of these 85 had positive Kveim and/or other tissue histology; six had erythema nodosum with bilateral hilar lymphadenopathy (without positive histology) and eight had no histology and did not fulfil the diagnostic criteria for this study. Therefore, the information in this report is based on 91 patients. The result of Kveim tests was available in 42 cases of which 37 were positive and five negative. Many more had Kveim tests but the results were not documented. Histology from tissue biopsy was available in 70 cases many of whom also had positive Kveim tests. Five with negative Kveim tests had reports of positive histology done elsewhere.

There was sufficient information in the notes of 76 patients to comment on tuberculin sensitivity. No consistent strength of tuberculin had been used for the Mantoux testing, 1, 10 or 100 TU being used in different patients. 59 patients were Mantoux tested, of whom 10 were negative to 1 TU, 17 to 10 TU and 15 to 100 TU. In 10 patients the skin test was negative but the strength of Mantoux used was not recorded, and seven patients had positive Mantoux tests. 13 patients had negative Tine tests and three had negative Heaf tests. One patient had a positive Tine test.

Most patients fell into one of two ethnic groups—West Indian and Caucasian—although eight were of other origins (seven African and one Indian) (Table I). Sex distribution was equal in the West Indians but there were slightly more females in the Caucasian group. Two patients in the Caucasian group were of Irish origin. Of the 36 patients of West Indian origin all but one were immigrants. It was possible to determine the interval between year of arrival in the UK and the age of presentation from the notes of 24 of these. The average interval was 13.6 years (range of 9–24 years). The year of arrival in the UK of 11 patients was not recorded.

The mean age of onset of those symptoms which were attributed by the clinician to sarcoidosis was 35.7 years in Caucasians and 41.4 years in West Indians and this difference is statistically significant ($P < 0.05$), although the ranges were large.

Many series have been published in which a high proportion of patients were asymptomatic and diagnosis was made by routine chest radiograph. However this was an

Table I. Sex distribution and ethnic groups

Sex	*West Indian*	*Caucasian*	*Others**	*Total*
Male	18	19	7	44
Female	18	28	1	47
Total	36	47	8	91

* 6 West African, 1 East African, 1 Indian.

unusual mode of discovery of sarcoidosis in our study (only four patients) and the month of onset of symptoms was recorded in the notes of 88%. The distribution of the month of onset of symptoms was uneven, with more patients first developing symptoms in the months November to February and fewer in the months September and October (Fig. 1). This trend was similar in the two main ethnic groups and the differences in paired months of onset were significant ($P < 0.02$), even allowing for the relatively small numbers involved. There were no other known variables affecting the time of year that the patients were referred to our clinics.

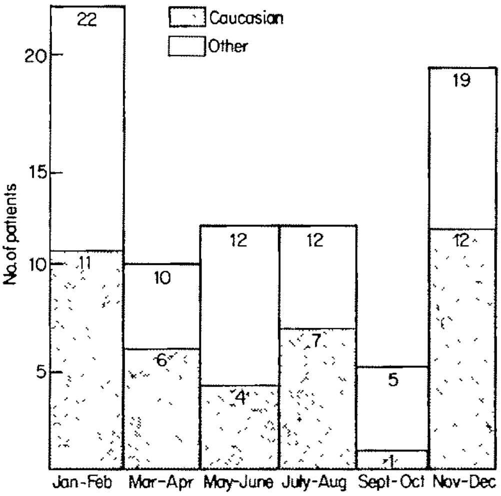

Fig. 1. Month of onset of symptoms. For number of patients *v.* expected distribution $\chi^2 = 14.39$; DF=5; $P < 0.02$

The commonest presenting symptoms (Table II) were respiratory (48%), i.e. cough, dyspnoea, chest discomfort or pain. It is interesting that West Indians presented with chest symptoms more frequently than Caucasians ($P < 0.05$) and particularly with retrosternal discomfort or occasionally pain. Constitutional symptoms, such as weight loss, fever or malaise, occurred in 32% of patients. Erythema nodosum occurred in 22% but in only one of the 36 West Indian patients compared with 19 of the 47 Caucasians. This difference is highly significant ($P < 0.001$). The well-known higher incidence of erythema nodosum in females (James 1961) was seen in the Caucasians.

Organs involved clinically or radiographically at any stage of the disease showed interesting variations (Table III). There appeared to be no difference between the ethnic groups in the length of follow-up. Eye involvement, confirmed by slit-lamp examination (which was performed on the majority of the patients), occurred in 24% of the total group, and was found significantly more often in the West Indian patients ($P < 0.01$).

Palpable lymphadenopathy was present in 44% of the total group of patients and was far commoner in the West Indians ($P < 0.001$). No accurate record of the exact sites of the palpable lymph nodes was available in many records. A palpable spleen was present in 18% and this, too, seemed to be commoner in West Indians although numbers were too small to draw firm conclusions. On analysing the number of extrapulmonary organs

Table II. Symptoms at presentation

Symptom	*West Indian*		*Caucasian*		*Others*	
	Male	Female	Male	Female	Male	Female
Constitutional: fever, malaise, weight loss	7	5	8	5	4	0
Chest:						
Cough, dyspnoea	2	2	2	6	0	0
Discomfort or pain	11	8	5	5	3	0
Eye discomfort	2	4	2	0	0	0
Peripheral lymphadenopathy	0	3	1	3	1	0
Erythema nodosum	0	1	3	16	0	0
Other skin lesions	1	3	0	1	1	1
Parotitis and/or cranial nerve lesion	2	2	0	0	1	0
Chance chest X-ray finding	1	0	1	2	0	0
Arthralgia	4	6	8	8	2	0

* Many patients had several symptoms at presentation.

Table III. Organs involved clinically or radiographically

Involvement of	*West Indian*		*Caucasian*		*Others*	
	Male	Female	Male	Female	Male	Female
Lungs	18	16	18	26	6	1
Eyes	7	9	2	3	1	0
Palpable lymph nodes	11	12	3	6	5	1
Spleen	5	3	3	1	3	0
Liver	7	2	4	1	2	0
Erythema nodosum	0	1	3	16	0	0
Other skin involvement	2	8	2	3	1	1
Parotid	2	1	0	1	0	0
Cranial or peripheral neuropathy	0	2	2	3	1	0
Bone	2	2	0	0	0	0

involved clinically at presentation or during follow-up (Table IV) (excluding erythema nodosum or arthralgia as 'organs'), the disease was significantly more widespread in West Indians ($P < 0.001$). The initial radiographic appearances are shown in Table V. Bilateral hilar node enlargement (stage 1) was seen more commonly in Caucasians but this difference did not reach the level of statistical significance.

The patients were under the care of several different physicians whose indications for steroid treatment varied and hence comparison between groups must be guarded. However, slightly over half of the patients were treated with systemic steroids.

Table IV. Number of extrapulmonary organs involved at any time during follow-up (excluding arthralgia and erythema nodosum)

No. of extrapulmonary organs	*West Indian**	*Caucasian**	*Others*
0	7	27	0
1	10	10	2
2	2	7	4
3	17	3	2
Total	36	47	8

* $\chi^2 = 23.1$; DF=4; $P < 0.001$.

Table V. Appearance of initial chest radiograph

Radiographic appearances	*West Indian*	*Caucasian*	*Others*	*Total*
Normal	2	3	1	6
Bilateral hilar lymph-node involvement	17	29	4	50
Bilateral hilar lymph-node involvement with pulmonary infiltration	12	12	2	26
Pulmonary infiltration without bilateral hilar lymph-node involvement	5	3	1	9

DISCUSSION

There have been studies of sarcoidosis from many parts of the world where immigrants have been found to be suffering from the disease, e.g. the Martinique population in Paris, Puerto Ricans in New York and Mexicans in Los Angeles (Silzbach et al. 1974). This survey has revealed facts about the manifestations of sarcoidosis seen in people of different ethnic groups who have come to live in south-east London. There is no reason to suppose that the likelihood of being referred and admitted to hospital differed between ethnic groups, therefore, the results are representative and comparable.

Variations in clinical expressions of sarcoidosis have been shown in this study; the patients of West Indian origin in London appear to develop the disease later, show differences in presenting symptoms and the type and extent of organ involvement. The frequency of chest symptoms in this study (48%) is higher than in some others, e.g. 19% of Silzbach's group (1967), but similar to 52% of another series (Maycock et al. 1963). Hendrick et al. (1976) have recently emphasized that, although chest pain is usually regarded as an unusual feature of sarcoidosis, it may be the predominant symptom. A dull central chest pain may be related to enlargement of hilar or mediastinal lymph nodes as has been suggested in patients with lymphomas (Anderson & Broughton 1957). In my study chest pain and peripheral lymphadenopathy were both significantly commoner in blacks and hilar and mediastinal lymphadenopathy may also have been more prominent.

Erythema nodosum was uncommon in the West Indian group, but occurred in nearly a quarter of Caucasians, particularly females. 100 cases of sarcoidosis have recently been reviewed from Jamaica (Lowe 1978) where no cases of erythema nodosum were found. Skin sarcoidosis is a separate entity from erythema nodosum and is usually persistent with histology showing typical infiltration with sarcoid granulomas. This series suggests that skin sarcoidosis is commoner in West Indians but the numbers are too small to permit firm conclusions. These differences between ethnic groups in the occurrence of erythema nodosum and possibly skin sarcoidosis might be relevant to the long-term prognosis of the two groups. It is known that erythema nodosum with bilateral hilar lymphadenopathy has a very favourable prognosis (Løfgren 1953), whereas skin sarcoidosis, particularly lupus pernio, is frequently accompanied by lung changes progressing to pulmonary fibrosis (Scadding 1967).

Eye involvement (24%) in this study is less than the 33% of Crick et al. (1961) but similar to the 22% quoted from a worldwide series (Silzbach et al. 1974). Eye involvement was commoner in the West Indians and in the USA blacks also have more frequent eye involvement (Sartwell & Edwards 1974).

Silzbach (1967) reported involvement of three or more organs as a bad prognostic factor and Sartwell (1976) noticed that blacks in the USA tend to develop a more disseminated disease. This present study has shown a highly significant difference between West Indians and Caucasians in the degree of organ involvement as assessed clinically or radiologically over similar periods of follow-up.

A seasonal variation in the month of onset of symptoms was observed in this study and in a large survey from Japan (Hosada et al. 1976). Seasonal variations of erythema nodosum (most due to sarcoidosis) has been reported by James (1961). These trends, although not in concordance as far as season of onset is concerned, nevertheless suggest that environmental factors may be important.

The results from the group as a whole make an interesting comparison with other surveys. Smellie and Hoyle (1960) reported that 58% of their patients were discovered by routine chest radiograph compared with only 4% of the present group. This is a reflection of the use of mass chest radiograph screening programmes which had been stopped before the majority of this group was diagnosed. A high prevalence of asymptomatic and hence normally undetected sarcoidosis may alter the mean age of onset of the disease and the paucity of chance diagnosis by radiograph in this group may explain why the mean age of onset is later than that in many series which have shown the peak incidence to be in the 20–35 year age range (Silzbach 1967; Maycock et al. 1963), although there are reports of later mean ages of onset (Carr & Gage 1954; Djuric 1976). West Indians showed a significantly later mean age of onset of symptoms compared with the Caucasian group, which might be explained by their later exposure to an environmental agent.

The degree of hyperglobulinaemia in sarcoidosis is more marked in blacks than whites (Israel & Washburne 1978). James et al. (1975) found raised IgG and IgM levels more common in West Indians than Caucasians which suggests a quantitative difference in the response of the humoral antibody system, although it is known that some apparently healthy West Indians may have high levels of IgG. Studies of patients with sarcoidosis have shown that those who have the inherited antigen HLA-B8 are more likely to develop arthritis and/or erythema nodosum (Brewerton 1978). In one series (Neville et al. 1978) in the UK, it was found that erythema nodosum occurred in 31% of Caucasian sarcoidosis patients whilst HLA-B8 occurs in 29% of the general population. Japanese patients, like West Indians, rarely have erythema nodosum (4%) and HLA-B8 is present in less than 2% of their general population. Differences in the prevalence of the inherited antigen HLA-B8 in West Indians might explain some of the findings in this study.

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Requests for reprints to: Dr D. Honeybourne, King's College Hospital, London.

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TWO ORAL BETA-ADRENERGIC STIMULANT DRUGS, PIRBUTEROL AND SALBUTAMOL, IN REVERSIBLE AIRWAY OBSTRUCTION*

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Summary

Pirbuterol and salbutamol capsules were compared in a multi-centre, double-blind, crossover study. Pirbuterol 10 mg four times daily and salbutamol 4 mg four times daily produced a similar increase in peak expiratory flow rate, matched by the patients' subjective appreciation of decreased breathlessness. Both drugs produced the same incidence of tremor.

INTRODUCTION

Willey et al. (1976) found pirbuterol an effective oral bronchodilator in single doses of up to 20 mg. Pirbuterol (15 mg) and salbutamol (4 mg) produced equal peak bronchodilatation. Pirbuterol is not yet commercially available and 10 mg four times daily was the maximum dose approved for regular administration when the present study was designed, although higher doses can now be used. Accordingly this dosage and a lower one of 10 mg thrice daily were included in this study to determine the acceptability of the chosen doses of pirbuterol, to detect adverse effects and to compare it with salbutamol.

Patients and Methods

Patients aged 16 or over, showing 20% or greater improvement in forced expiratory volume in one second (FEV_1) after 160 μg of inhaled isoprenaline, were studied. Those in unstable clinical state or with other systemic diseases were ineligible. Patients stabilized on corticosteroids or sodium cromoglycate were included. Bronchodilators other than a salbutamol inhaler for additional symptomatic relief were stopped.

The study was conducted double-blind in 27 centres. In the first week the patients took two placebo capsules thrice daily. In the second week they took two active capsules thrice daily, by random allocation either pirbuterol 30 mg a day or salbutamol 12 mg a day. Reformulation of commercially available Ventolin tablets as salbutamol capsules did not affect their bioavailability (Henderson 1977). In the third week they took two capsules four times daily: pirbuterol 40 mg a day or salbutamol 16 mg a day. The more acceptable of the two doses was taken for a further eight weeks. A cross-over to the comparable dose of the other drug took place for the final two weeks.

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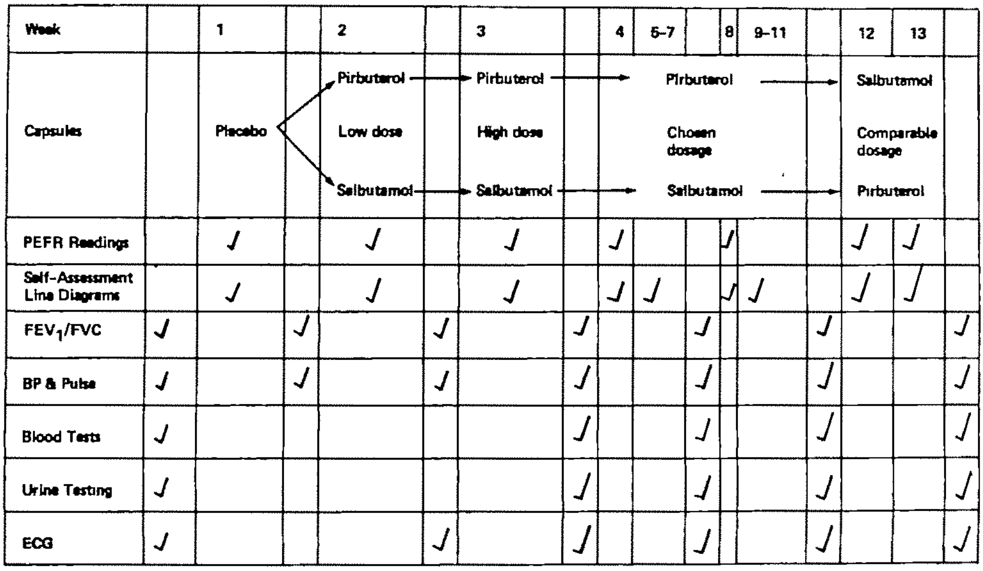
* This study was designed and coordinated by Dr A. J. Dyson, Research Fellow, on behalf of the Clinical Trials Sub-Committee of the British Thoracic Association, whose members were: Elizabeth A. Hills and A. R. Somner (chairmen); K. M. Citron, T. J. H. Clark, Sir John Crofton, P. C. Elmes, J. A. R. Friend, R. M. Greenwood, and A. Pines. The report was prepared by Dr A. D. Mackay, whose Research Fellowship was also supported by the Chest, Heart and Stroke Association.

The timing of measurements made during the study is summarized in Fig. 1. The patients recorded two peak flow gauge readings thrice daily before treatment and daily usage of inhaled salbutamol during the weeks indicated. They made daily self-assessments on line diagrams of breathing, sleep, awareness of palpitations, steadiness of hands, and impression of well-being throughout the study.



Week		1		2		3		4	5–7		8	9–11		12	13	
Capsules		Placebo		Pirbuterol → Low dose Salbutamol →		Pirbuterol → High dose Salbutamol →		Pirbuterol → Chosen dosage Salbutamol →						Salbutamol Comparable dosage Pirbuterol		
PEFR Readings		✓		✓		✓		✓			✓			✓	✓	
Self-Assessment Line Diagrams		✓		✓		✓		✓	✓		✓	✓		✓	✓	
FEV_1/FVC	✓		✓		✓		✓			✓			✓			✓
BP & Pulse	✓		✓		✓		✓			✓			✓			✓
Blood Tests	✓						✓			✓			✓			✓
Urine Testing	✓						✓			✓			✓			✓
ECG	✓				✓		✓			✓			✓			✓

Fig 1. Measurements made during the study and their timing

RESULTS

Ninety-five patients entered the study; 23 were withdrawn. Sixteen withdrawals were unrelated to either active drug, occurring whilst on placebo or being due to failure to fulfil the protocol. Three patients withdrew while on the lower dose of salbutamol: one developed muscle cramps, one tremor and one an exacerbation of asthma requiring oral corticosteroids. Four patients withdrew while on pirbuterol: all had tremor and two of these palpitations. Two were taking 30 mg and two 40 mg of pirbuterol a day. Seventy-two patients remained for analysis, 39 receiving oral or inhaled corticosteroids.

Thirty-eight patients received the sequence placebo–pirbuterol–salbutamol and 34 placebo–salbutamol–pirbuterol. Only two patients in each group reverted to the lower dosage during the study. These two groups were comparable in terms of percent predicted FEV_1, age, sex and initial steroid usage.

Steroid usage

Seventeen of the 72 patients had exacerbations of asthma and were given a short course of corticosteroids tablets or an increase in maintenance dosage. In ten this occurred whilst on salbutamol, in six whilst taking pirbuterol and in one during both treatments. Because of the complicating effect of corticosteroid courses these patients are excluded from the analysis which follows.

Peak expiratory flow rate and spirometry

For the appropriate weeks mean peak expiratory flow rate (PEFR) was calculated after excluding the readings within four hours after salbutamol inhalation. The mean of the readings for Weeks 4 and 8 when taking the first drug was compared with the mean for Weeks 12 and 13 (the cross-over period). Similarly the mean of the FEV_1 and the FVC readings at the end of Weeks 7 and 11 was compared with those from the end of Week 13. Mean results for PEFR and FEV_1 are shown in Fig. 2.

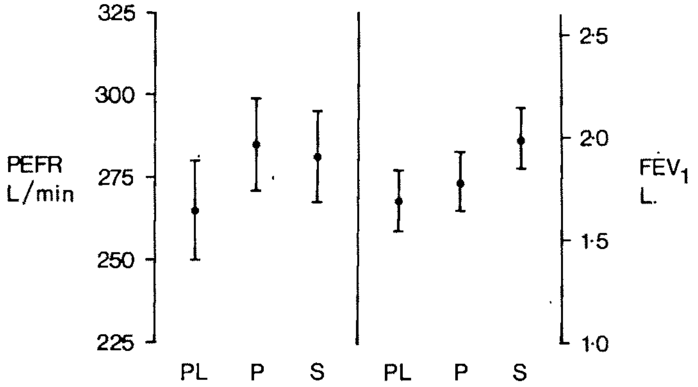


Fig. 2. Means and standard errors for PEFR and FEV_1 on placebo (PL), pirbuterol (P) and salbutamol (S) in 55 patients

Using Student's paired *t*-test on within-patient differences, there was a statistically significant increase in PEFR compared with placebo on both pirbuterol ($P < 0.005$) and salbutamol ($P < 0.01$) but no significant difference between pirbuterol and salbutamol.

Salbutamol produced a statistically significant increase in both FEV_1 ($P < 0.005$) and and FVC ($P < 0.02$) compared with placebo, whereas the increases after pirbuterol were not significant.

Subjective assessments

Using the signed rank sum test there were statistically significant improvements compared with placebo in breathing on both treatments ($P < 0.001$), an overall impression of well-being on both pirbuterol ($P < 0.02$) and salbutamol ($P < 0.01$) and a statistically significant decrease in nocturnal symptoms on both pirbuterol ($P < 0.01$) and salbutamol ($P < 0.05$).

Salbutamol inhaler usage

The mean number of puffs of salbutamol used per week was 23 on placebo, 19 on pirbuterol and 20 on salbutamol.

Pulse and blood pressure

These did not change significantly.

Biochemical tests

There was elevation of creatine phosphokinase in 19 out of 93 patients. Six patients showed an abnormal value on pirbuterol, six on salbutamol and seven showed abnormal values during both treatments.

ECG traces

Two patients showed ventricular ectopics which had not been recorded at entry. One was taking salbutamol and one pirbuterol, both in the higher dosage.

Unwanted effects

There were 19 instances of tremor (pirbuterol ten, salbutamol nine) and ten of palpitations (pirbuterol six, salbutamol four).

DISCUSSION

As maintenance therapy, pirbuterol 10 mg four times daily proved as effective as salbutamol 4 mg four times daily, judged by increase in PEFR measured thrice daily. Although neither bronchodilator appreciably diminished usage of the salbutamol inhaler from that on placebo, the clinical value of the improvements in PEFR was emphasized by the subjective assessments.

Paterson et al. (1977) reported on 16 patients who received oral pirbuterol 10 mg four times daily for 12 weeks after four weeks on placebo, and showed no significant overall symptomatic improvement. In contrast, this study demonstrated statistically significant improvements in symptoms on the same dosage.

Tremor is a well reported side effect of oral salbutamol (Legge et al. 1971: Parker et al. 1971). Pirbuterol showed no superiority in this respect.

Pirbuterol appears as effective as salbutamol when an oral sympathomimetic bronchodilator is prescribed.

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Requests for reprints to: Dr A. D. Mackay, Faculty of Medicine, Southampton General Hospital, Tremona Road, Southampton, SO9 4XY, from whom the detailed results of the study may also be obtained.

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CLARA CELLS IN LLAMAS BORN AND LIVING AT HIGH AND LOW ALTITUDES

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Summary

Quantitative histological studies showed greater Clara cell activity in two llamas born and spending their lives in the High Andes as compared to a llama born and spending its life at sea level.

INTRODUCTION

The Clara cell is a non-ciliated cell which occurs in the bronchioles. It appears to be secretory, the product of secretion accumulating within smooth cisternae at the apex of the cell. The apical region is then extruded into the bronchiolar lumen in a process of apocrine secretion (Fig. 1). The function of Clara cells is still not established and hence it seems worthwhile to report a striking difference in their activity in the same species exposed to two different natural environments. Accordingly we report here our quantitative findings on the activity of Clara cells in llamas born and bred at high altitude in the Andes and at sea level at Chester Zoo in Britain.

Method and Materials

We studied three llamas. Two of them (L1 and L2) had been born and lived all their lives on an *estancia* at Rancas which is situated at an altitude of 4720 m above sea level in the Peruvian Andes. At this elevation the atmospheric pressure is 425 mmHg and the partial pressure of oxygen in the ambient air is 82 mmHg. One of these animals was male (L1) and the other female and pregnant (L2); both were two years old.

The third llama (L3) was born in Chester Zoo and lived its entire life at sea level, dying at the age of 9½ years shortly after having delivered an offspring. It had thus been exposed all its life to an atmospheric pressure of 760 mmHg with a partial pressure of oxygen in the ambient air of 159 mmHg. Thus we were able to study two llamas which had been born and lived all their lives at high altitude, and a llama which had been born and lived all its life at sea level.

Llamas L1 and L2 were killed on the mountainside at Rancas in the Andes and the lungs removed and taken to the High Altitude Research Station at Cerro de Pasco, a few kilometres distant. There the right lungs were distended with 10% formol saline until the pleural surfaces were smooth. The lungs were cut into slices 2 cm thick after fixation and these were transported to Liverpool for histological study. Blocks of lung were resected and paraffin sections 5 μm thick were cut and stained with haematoxylin and eosin. The low altitude llama (L3) died at Chester Zoo. The right lung was removed and transported to the Department of Pathology at Liverpool University where it was fixed and subsequently processed in an identical manner to that employed for the high-altitude camelids.

In the sections of lung those Clara cells in the terminal bronchioles which had been active at the moment of death of the animal were easily identifiable with their mushroom-shaped or club-shaped apical caps which projected into the lumen of the bronchiole (Fig. 2A). The cytoplasm of the base of the cell was somewhat basophilic and that of the apical cap was vesicular due to dilatation of the endoplasmic reticulum of this region of the cell recognized by electron microscopy in a previous investigation (Heath et al. 1976). In some Clara cells the club-shaped apical caps were attached to the basal, nucleated portion of the cell by only a long, narrow isthmus (Fig. 2B). In recesses in the bronchiolar epithelium some of the apical caps appeared to have fused to form a syncytium. In some areas apical caps had been extruded to lie free in the bronchiolar lumen. The appearances were consistent with cellular apocrine secretion.

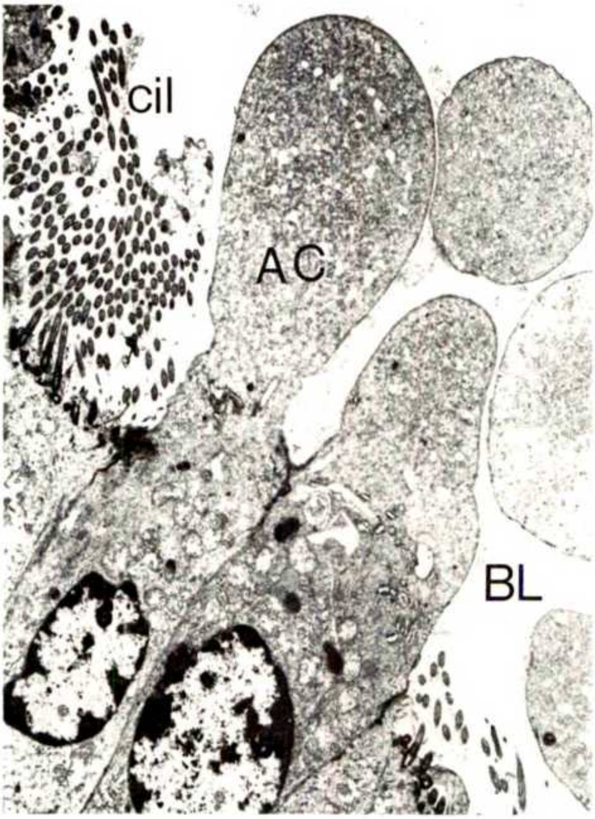

Fig. 1. Electron micrograph of terminal bronchiole of one of the llamas (L1) which had been born and lived its entire life at an altitude of 4720 m in the Peruvian Andes. There is pronounced activity of the Clara cells so that apical caps (AC) project into the lumen and eventually become extruded into the bronchiolar lumen (BL). The Clara cells are surrounded by respiratory epithelial cells whose cilia (cil) can be clearly seen. × 4400

The Clara cells were so characteristic in appearance as to be readily identifiable and thus they proved to be easy to count. Accordingly sections of lung from the high- and low-altitude camelids were studied systematically using a Reichert-Jung Visopan Projection Microscope with a × 40 objective so that every strip of bronchiolar epithelium in successive microscopic fields coming into view was measured by planimetry. In order to assist planimetry the viewing screen was covered with tracing paper so that the planimeter wheel could make a firmer grip. After this the number of attached and free apical caps present in that strip was counted. In this way the total length of bronchiolar strip examined for each animal was summated, together with the total number of Clara cell caps counted (Table I). In this way also the number of Clara cells per mm of bronchiolar strip was calculated (Table I).

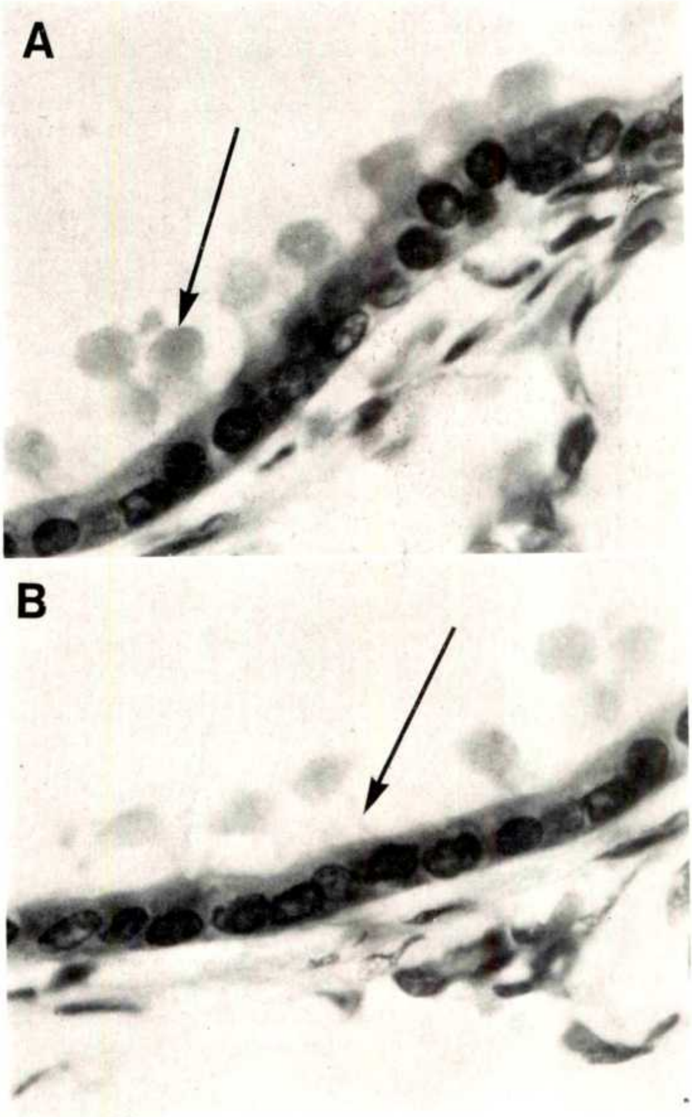

Fig. 2. Bronchiolar epithelium from the same high-altitude llama. A, Mushroom-shaped Clara cells (arrow) which project into the lumen. B, Apical caps about to be extruded and connected to the basal portion of the cell by an isthmus (arrow). Haematoxylin and eosin, ×1180, under oil

RESULTS

The immediate impression gained from microscopic examination was that there were more active Clara cells in the llamas from the Andes (Fig. 2) than in that from Chester Zoo (Fig. 3). This was subsequently confirmed by counts of Clara cell caps in lengths of bronchiolar epithelium. The age, sex and origin of each of the llamas is shown in Table I, together with the total number of Clara cell caps counted and the number per mm of

Table I. Quantitative assessment of Clara cell activity in high- and low-altitude llamas

	Llama		
	L1	L2	L3
Sex	M	F	F
Age (years)	2	2	9½
High or low altitude	H	H	L
Length of bronchiolar strip examined (mm)	53.5	66.7	50.7
No. of Clara cell caps	2905	7104	426
No. of Clara cell caps/mm	53.4	106.4	8.4

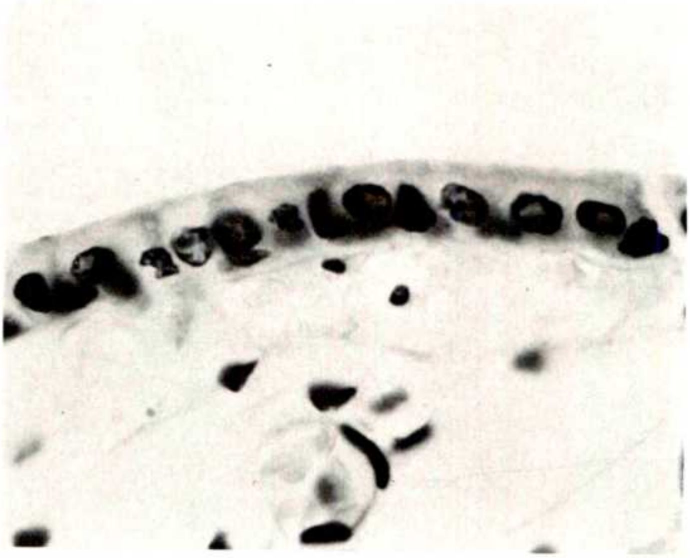

Fig. 3. Bronchiolar epithelium from a llama (L3) which had been born and lived its entire life at sea level, eventually dying in Chester Zoo. The epithelium is quiescent, there being a total absence of Clara cell caps. Haematoxylin and eosin, × 1180, under oil

bronchiolar epithelium. The number of animals studied is too small to be susceptible to statistical analysis. However, the data gathered appear to be worthy of report since there seems little likelihood of having access to material from larger numbers of high-altitude llamas killed on the side of an Andean mountain, or from larger numbers of low-altitude representatives of the species dying in zoos at sea level.

Discussion

Our study of this small group of camelids suggests that hyperactivity of the Clara cells is a feature of the environment rather than the species for it was found in only the two high-altitude llamas. The extrusion of the apical caps of these cells and their contained secretion into the bronchiolar lumen appears to be advantageous for life in the mountain environment which differs in several respects from that of sea level (Heath & Williams 1977). The mountain air is less humid and life is exposed to increased solar, ultra-violet and cosmic radiation. Above all, the reduced barometric pressure of the high mountains leads to chronic hypoxaemia. Thus our two llamas from Rancas were subjected all their lives to a partial pressure of oxygen in the ambient air only half of that found at sea level.

We have previously noted an acceleration of the process of extrusion of the apical caps of Clara cells in adult Wistar albino rats subjected to a subatmospheric pressure of 265 mmHg for 12 hours, this reducing the partial pressure of oxygen to only 56 mmHg (Smith et al. 1974). In such conditions which simulated an altitude of 8000 m, approaching the summit of Mount Everest, the apical caps contained an excess of smooth endoplasmic reticulum.

Autoradiographical studies have suggested that the extensive smooth endoplasmic reticulum of Clara cells contains accumulations of a phospholipid, dipalmitoyl lecithin which is a known pulmonary surfactant, lowering surface tension in the lung (Etherton et al. 1973). The histochemistry of Clara cells suggests that they contain lipoproteins rich in choline-containing phospholipids likely to be pulmonary surfactant (Azzopardi & Thurlbeck 1969). There has been one report (Castillo & Johnson 1969) that there is an increase in surface tension of lung extracts of mice after their acute exposure to a simulated altitude of 4270 m for 45 minutes. However, this suggestion that exposure to acute hypoxaemia may demand an increased production of pulmonary surfactant has been criticized on the grounds that the sonication technique used by Castillo and Johnson (1969) would release much cellular lipid. Since surfactant lipids account for only 5–10% of the total they would tend to be swamped by the tissue lipids (Clements 1976). Thus according to Clements (1976) the surface tension area loops shown in the paper of Castillo and Johnson (1969) are predictable from knowledge of the extraction procedure; they are not specific to lung surfactant. Hence before the suggestion that high altitude increases alveolar surface tension can be accepted, confirmation of their work must be forthcoming from other workers using techniques not open to these objections. Furthermore, it has to be kept in mind that the increase in surface tension was demonstrated in unacclimatized mice whereas in this paper we are dealing with species showing a remarkable adaptation to the hypoxaemia of high altitude.

From a biophysical standpoint, since the difference in pressure necessary to inflate the alveolar sacs against the elasticity of the alveolar walls and surface tension of the alveolar fluid is independent of the ambient air pressure, it is difficult to explain the need for more pulmonary surfactant in these animals.

It has to be kept in mind that it has not yet been established whether the extruded apical caps of the Clara cells perform their function in the alveolar space or in the bronchial tree itself. Mountain air is dry and cold and the low humidity is a cause of respiratory discomfort at high altitude (Heath & Williams 1977). In these circumstances the copious production of a mucoid material would be advantageous. Whether this is the significance of increased Clara cell activity as originally suggested by von Hayek (1962) or whether there is a more specific biochemical function we do not know. Similarly it cannot be denied that in the three animals we studied there was a high Clara cell count in the two young llamas aged two years and a low count in the older animal aged 9½ years. This could be held to be consistent with decreasing Clara cell activity with increasing age. Despite these reservations, however, we still feel that this striking difference in the activity of these cells in high- and low-altitude llamas is worthy of note.

ACKNOWLEDGEMENTS

We wish to thank Dr H. Krüger of the Cayetano Heredia Medical School of Lima, Peru, for his help with the study of the two high-altitude llamas. We are most grateful to the North of England Zoological Society, Chester, for allowing us to study tissues of the llama shortly after its death.

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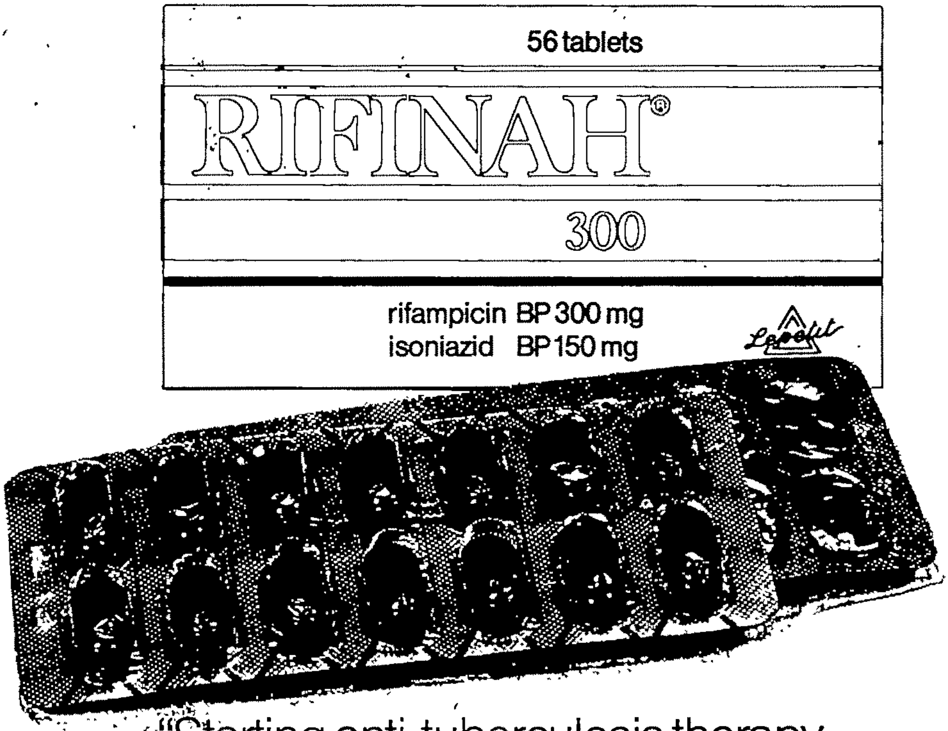

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A COMPARISON OF BIOPSY RESULTS USING RIGID AND FIBREOPTIC BRONCHOSCOPES

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Summary

A comparison of the results of bronchial biopsy in the histological diagnosis of lung cancer obtained via the fibreoptic bronchoscope and the rigid bronchoscope has been made. Positive biopsy rates of 72% with the fibreoptic bronchoscope and 51% with the rigid bronchoscope were obtained ($P < 0.001$). Evidence is presented to show that this difference was not due to selection of patients. The negative biopsy rates in the presence of proven visible tumour were 9% with the fibreoptic bronchoscope and 16% with the rigid bronchoscope.

INTRODUCTION

In comparison with the rigid bronchoscope the fibreoptic bronchoscope is easier to pass into the bronchial tree and has a greater visual range of the bronchial tree (Kovnat et al. 1974). The increased visual range of the fibreoptic bronchoscope should theoretically increase the biopsy range and so increase the positive biopsy rate in lung cancer (Macdonald 1975). The biopsy forceps passed via the fibreoptic bronchoscope are very much smaller than those passed via the rigid bronchoscope and consequently provide much smaller samples (approx. 1–3 mm spheres) which are less easy to interpret histologically. The positive biopsy results in lung cancer reported with the fibreoptic bronchoscope by Ikeda (1974) and Zavala (1975) were 96% and 85% respectively and included samples for cytology obtained by brush biopsy and transbronchial biopsy techniques using fluoroscopic control as well as bronchial biopsy for histology. Norris (1948), Somner et al. (1958) and Oswald et al. (1971) obtained rates of 71%, 61% and 50% respectively using the rigid bronchoscope and again their samples were all bronchial biopsies for histology. Cytology is less reliable than histology in the diagnosis of lung cancer and requires considerable expertise in interpretation and for this reason we believe that the positive histological biopsy rate is the most reliable method of assessing the relative merits of the diagnostic value of the fibreoptic and rigid bronchoscopes in the diagnosis of lung cancer. In Fig. 1 the number of fibreoptic and rigid bronchoscopies performed at the Brompton Hospital in the years 1973–6 are shown. The numbers were comparable in the years 1974–5 and this situation is highly unlikely to occur again and for this reason we were in an ideal position to perform a direct comparison of the two techniques using a pathology service and biopsy method common to both techniques. No comparison of these two techniques has been performed previously on a large series of patients.

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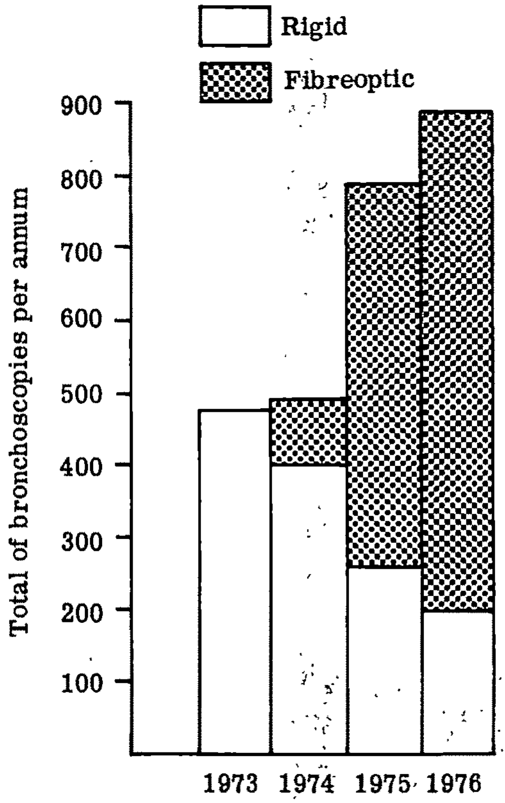

Fig. 1. Fibreoptic and rigid bronchoscopies performed at the Brompton Hospital, 1973–6

Methods

The notes of all the patients having bronchoscopies from July 1974 to June 1975 inclusive were obtained and the following details recorded from the notes:

1. The findings at bronchoscopy
2. The bronchial biopsy results
3. The final diagnosis

The fibreoptic bronchoscopies were performed transnasally under local anaesthetic (Smiddy et al. 1971) and the rigid bronchoscopies were performed under general anaesthetic.

RESULTS

273 fibreoptic and 325 rigid bronchoscopies were performed. Details of the findings in lung cancer are given in Table I. The positive biopsy rates were 72% (fibreoptic) and 51% (rigid), $P < 0.001$. The negative biopsy rates in the presence of visible proven tumour were 9% (fibreoptic) and 16% (rigid). These proportions were not significantly different.

DISCUSSION

Selection of patients in the two groups was not thought to be biased in favour of the fibreoptic group for the following reason. Each of the fibreoptic bronchoscopic biopsy

Table I. Comparison of fibreoptic and rigid bronchoscopy biopsy rates in lung cancer

	Fibreoptic	*Rigid*
No. of bronchoscopies	273	325
No. of cases of primary lung cancer	95	164
No. of positive biopsies	68	83
Positive biopsy rate	72%	51% ($P < 0.001$)

sites was indicated on a diagram of the bronchial tree on the fibreoptic bronchoscopy report form. Twenty-three of the 68 positive biopsies were assessed to have been out of biopsy range of the rigid bronchoscope. The location of the 23 biopsies is shown in Table II. If these 23 positive biopsies are subtracted from the 68 a positive biopsy rate of 47% is obtained [(68 − 23) ÷ 95 = 47%]. This is not significantly different from the positive biopsy rate achieved in the rigid bronchoscopy series. This is indirect evidence that the two groups were comparable and we believe that the difference in the biopsy rates using the two techniques reflects the diagnostic superiority of the fibreoptic bronchoscope resulting from the increased biopsy range.

Table II. Location of 23 fibreoptic series biopsies positive for lung cancer judged to be out of range of the rigid bronchoscope

Location	*No.*
Segmental level, left upper lobe	14
Segmental level, right upper lobe	6
Apical segment of right lower lobe	1
Apical segment of left lower lobe	1
Left lower lobe of bronchus (previous rigid bronchoscope)	1
Total	23

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SYSTEMIC AMYLOIDOSIS COMPLICATING CYSTIC FIBROSIS

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Amyloidosis complicating cystic fibrosis is rare. Two previous reports have appeared (Missmahl 1967; Ristow et al. 1977). A further case is reported here.

Case Report

A white male was diagnosed as suffering from cystic fibrosis at 18 months of age. He required regular Nutrizym tablets for pancreatic insufficiency but did not develop bronchopulmonary infections until he was 12 years old, when *Proteus mirabilis*, *Staphylococcus aureus* and *Pseudomonas aeruginosa* were isolated from his sputum. Hepatosplenomegaly was recorded when he was 17 years old and a year later liver and rectal biopsies confirmed amyloidosis. Intermittent proteinuria was noted.

Recurrent haemoptyses developed when he was 16 years old. Two years later he had a massive haemoptysis for which bronchial artery ligation was necessary. Small haemoptyses continued and in 1976 (he was 24 years old) a further bronchial artery ligation was necessary to stop bleeding from the left lung. In November 1976 he developed haematuria and loin pain and heavy proteinuria was recorded for the first time. This persisted and an intravenous urogram showed slightly enlarged kidneys.

In December 1976 he developed a persistent bronchopulmonary infection and *Proteus mirabilis* and *Ps. aeruginosa* were grown from the sputum. He was treated with gentamicin, carbenicillin and chloramphenicol but there was only a transient improvement and hospital readmission was necessary in January 1977. The infection failed to respond to antibiotics and he died soon after admission.

Laboratory investigations

Liver function. A raised alkaline phosphate (350 IU/litre) was first noted in 1971 and in 1976 it was 1500 IU/litre (normal range 20–90 IU/litre). Serum albumin was 35 g/litre in 1971 and 20 g/litre in 1976 (normal range 35–50 g/litre). Electrophoresis of serum in 1976 showed diminished albumin and raised globulin. There was no monoclonal band.

Renal function. Blood urea and creatinine remained normal. A trace of proteinuria was recorded in 1971 and 6 g proteinuria per 24 hours was noted in 1976. Bence Jones proteins were absent.

Other investigations. Chest radiograph showed hyperinflation, bronchial wall thickening and mottled shadowing in all zones. Sputum cultures grew *Proteus mirabilis* consistently and *Staph. aureus* and *Ps. aeruginosa* occasionally. *Aspergillus fumigatus* was never isolated from the sputum. Skin reactions to common allergens were all negative. Serum immunoglobulins were elevated: IgG 20 g/litre (normal 8–17 g/litre), IgA 4.8 g/litre (normal 1.5–4.5 g/litre) and IgM 1.83 g/litre (normal 0.45–1.45 g/litre). Blood sugar was normal.

Post mortem

Macroscopic and microscopic analysis revealed amyloidosis affecting the liver and kidneys (severely), parathyroid, thyroid, pancreas, spleen and pituitary. Patchy distribution was seen in the gastrointestinal tract. The tongue, heart and lungs appeared free from amyloid. The lungs showed severe bronchiectasis and a terminal bronchopneumonia.

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DISCUSSION

Amyloidosis is seen in patients with chronic infections such as syphilis, tuberculosis, chronic osteomyelitis and bronchiectasis (Brownstein & Hedwig 1971; Wiman & Hofer 1974), and also in chronic inflammatory conditions such as rheumatoid arthritis. Andersen (1938) did not mention amyloidosis as complicating cystic fibrosis in her series of autopsies of children with cystic fibrosis. Neither Landing (1962) nor Esterly et al. (1976) was able to find a case of amyloidosis complicating cystic fibrosis and only recently has a case report been published in the English literature (Ristow et al. 1977).

One reason why amyloidosis is so rare in cystic fibrosis could be that patients succumb to the disease before amyloidosis has had time to develop. However, this explanation is probably incorrect for the mean survival from diagnosis of patients with cystic fibrosis now exceeds 15 years. Bronchopulmonary infection occurs at an early age for in autopsies of children who had died from cystic fibrosis all those aged one year and over had evidence of chronic pulmonary infection (Esterly et al. 1976). Amyloidosis occurs in children with other diseases and Trasoff et al. (1944) found six cases of amyloidosis in patients under ten years of age. Amyloidosis may develop within a short time and Hoffman et al. (1951) described this as a complication of a chronically infected burn in a child of 2½ years.

Amyloidosis is known to occur in hyperactive immune states. There is now increasing evidence that an overactive immune state occurs in patients with cystic fibrosis. High levels of circulating immunoglobulins (Schwartz 1966), increased prevalence of skin reactions to common allergens (McCarthy et al. 1969) and a high prevalence of serum precipitins to *A. fumigatus* (Warren et al. 1975) are all seen in patients with cystic fibrosis. It is therefore puzzling that amyloidosis is observed so rarely.

The clinical and laboratory data do not suggest any reason apart from chronic infection why this patient with cystic fibrosis developed amyloidosis. The rarity of amyloidosis complicating cystic fibrosis remains unexplained.

ACKNOWLEDGEMENTS

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GONADOTROPIN-SECRETING BRONCHOGENIC CARCINOMA IN A WOMAN

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Summary

We report the case of a woman with a squamous carcinoma of the bronchus which secreted human chorionic gonadotrophin. Earlier reports have all involved males. Some evidence that estimation of serum HCG levels might prove a useful marker of early malignancy is presented.

INTRODUCTION

Ectopic production of human chorionic gonadotrophin can occur in patients with bronchogenic carcinoma (Becker et al. 1968; Cottrell et al. 1969; Daily & Marcuse 1969; Fusco & Rosen 1966; Faiman et al. 1967; Mochizuki et al. 1969) and often in patients with other cancers (Mukozima et al. 1974). Previous reports of ectopic human chorionic gonadotrophin production in lung cancer have all been in men, and we wish to report this disorder in a non-pregnant woman.

Case Report

A 74-year-old woman was admitted to hospital with rapidly increasing dyspnoea. The menopause had occurred 28 years before this admission and she had four children. She was emaciated and breathless. Gynaecomastia was absent. A chest radiograph confirmed the presence of a large right pleural effusion. On aspiration this yielded straw-coloured fluid containing malignant cells. An immunological pregnancy test was positive in urine, pleural fluid and serum. Human chorionic gonadotrophin levels were raised (Table I).

The patient died three weeks later. At post mortem there was a tumour originating from the right upper lobe and infiltrating the middle and lower lobes. Metastases were present in the hilar, mediastinal and axillary lymph nodes. Arising from the common hepatic duct was a tumour 1 cm in diameter which on histological examination was a well-differentiated papillary adenocarcinoma, a cholangioma. Microscopic examination of the lung tumour revealed that it was necrotic and haemorrhagic with a chorioncarcinoma-like appearance. In some regions there were sheets of cells with distinct intercellular bridges and some cells showed single cell dyskeratosis.

Examination by electron microscopy confirmed that the tumours cells arranged in sheets were connected to neighbouring cells by intercellular bridges consisting of cytoplasmic projections each containing a desmosome. Within the cytoplasm surrounding the cell nuclei was a network of abundant tonofibrils while the cells tended to undergo keratinization. The whole histological appearance was of a bronchogenic squamous carcinoma (Figs 1, 2, 3).

HCG levels were estimated at post mortem in a variety of tissues (Table I) using a radio-immunoassay test (Vaitukaitis 1973). The levels were abnormally high in the tumour tissue (2540 mIU/g) but normal in the opposite lung and in the cholangioma.

Table 1. Results of tests

Test			
Immunological tests for pregnancy			
Urine			
Gonavis	+	+	+
Gestate		4X	4X
Pleural fluids			
Gonavis		+	+
Gestate		–	–
Chorionic gonadotropin level (radio-immunoassay)			
Serum		257 ~ 540 mIU/ml	
Pleural fluids		490 mIU/ml	
Tissue extracts			
Tumour (lung)		2540 mIU/g	
Tumour (hepatic duct)		63 mIU/g	
Ipsilateral normal lung		23 mIU/g	

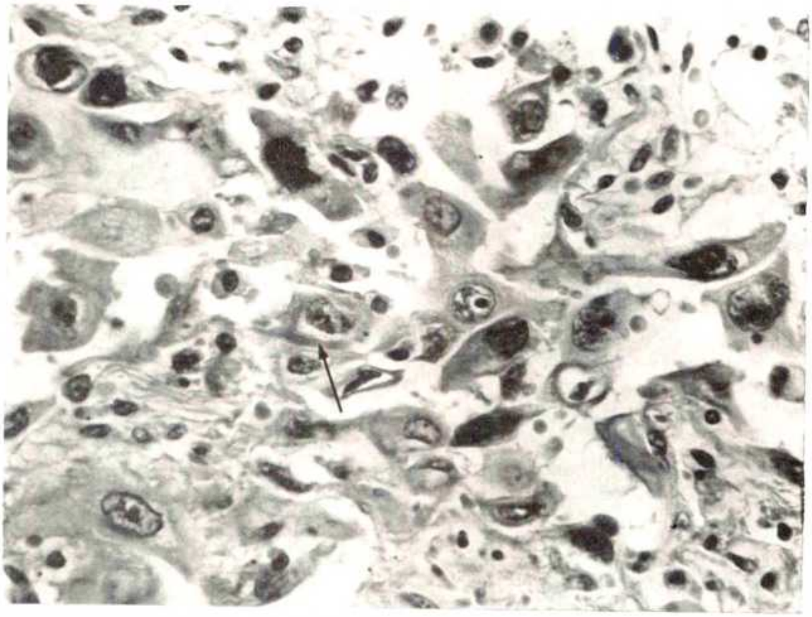

Fig. 1. Photomicrograph of lung showing epidermoid carcinoma. Note perinuclear halo and abundant eosinophilic cytoplasm (arrow). H & E × 520

DISCUSSION

A review of published cases of ectopic gonadotrophin-secreting tumours revealed that of 12 adults nine had lung cancer and all nine were men. The present report is of such a tumour in a woman where distinction from a chorioncarcinoma may present difficulties. In our patient there was no history of hydatid mole or teratoma and the patient had

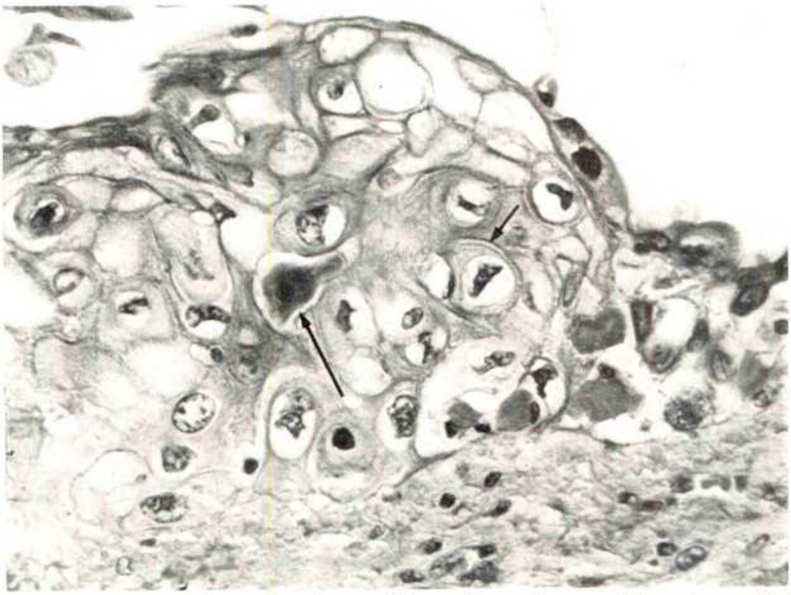

Fig. 2. Photomicrograph of lung showing epidermoid carcinoma. Note intercellular bridges (short arrow) and single cell dyskeratosis (long arrow). H & E ×520

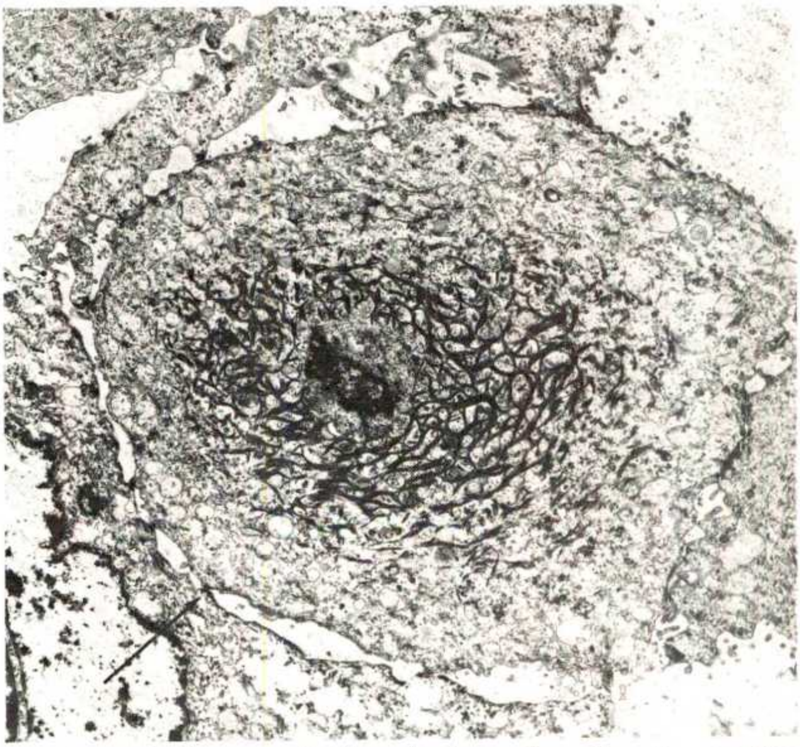

Fig. 3. Electronmicrograph of tumour cell of lung showing epidermoid carcinoma cell characterized by desmosomes and intercellular bridges. Uranyl and lead stain ×4500

passed the menopause 28 years before. Raised levels of HCG were present in pleural fluid, serum and in the tumour tissue and histological examination showed a squamous carcinoma.

Previously HCG-secreting tumours were regarded as rarities but the use of a highly sensitive and specific radio-immunoassay for HCG revealed high levels in 60 of 828 cases of non-testicular neoplasms (Braunstein et al. 1973). Mukozima et al. (1973) used the Hi-Gonavis test which has a sensitivity equal to that of radio-immunoassay and found raised levels of serum HCG in 34 of 251 patients with other sorts of tumours. In a single male patient with lung cancer the serum HCG level was raised for 13 months before the appearance of the lung cancer (Rosen et al. 1968) and it has been suggested that ectopic gonadotrophin secretion may serve as a marker for cancer (Sussman et al. 1974; Silva et al. 1974).

In the present patient there were no clinical manifestations of HCG secretion and possibly the tumour secreted subunits of HCG. HCG subunit production has been reported in tissue cultures of HCG-secreting lung cancer cells.

ACKNOWLEDGEMENT

We thank Professor M. Horino, Professor M. Nakagawa and Dr M. Mizushima for their help and advice.

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Short Communication

PREDNISOLONE PHARMACOKINETICS IN ASTHMATIC PATIENTS

C. S. May,* J. A. Caffin, J. W. Halliday and F. Bochner

The Prince Charles Hospital, Brisbane, and Department of Medicine, University of Queensland, Brisbane, Australia

Summary

Prednisolone serum levels have been measured by radio-immunoassay in 12 steroid-dependent asthmatic patients. Differences in prednisolone pharmacokinetics did not account for the variation in dose of prednisolone required to control asthma.

INTRODUCTION

Inter-individual differences in pharmacokinetics are an important factor in determining the dose of many drugs (Rawlins 1974). In the case of prednisolone, pharmacokinetics can differ widely between patients (Wilson et al. 1975; Tanner et al. 1979), as may the dose required to control airways obstruction in steroid-dependent asthmatic patients (Crofton & Douglas 1975). To determine if these findings are related, we have compared the pharmacokinetics of prednisolone in two groups of patients with asthma: those requiring 15 mg or more daily and those requiring less than 15 mg daily.

Materials and Methods

Twelve patients were studied (Table I). All had severe chronic extrinsic asthma requiring maintenance oral steroid therapy in addition to regular aerosol bronchodilators, oral theophylline and beclomethasone dipropionate and/or sodium cromoglycate by inhalation. In addition, Case 3 was taking methyldopa, frusemide, diphenylhydantoin and warfarin sodium, and Case 5 methychlothiazide. The daily dose of prednisone or prednisolone had been the same for at least three months before the study and is shown in Table I. Cases 1 to 6 were taking 15 mg or more daily ('high-dose') and Cases 7 to 12 less than 15 mg daily ('low-dose'). All patients gave informed consent.

The patients were fasted and took no prednisone or prednisolone for approximately 12 hours before the study. An initial blood sample was taken for radio-immunoassay for prednisolone (Caffin et al. 1978) and prednisolone 15 mg was then given by mouth. Repeat blood samples were taken at 0.5, 1.0, 2.0, 2.5, 3.0, 4.5, 6.0, 8.0, 10.0 and 12.0 hours after the dose. Food was allowed after three hours.

A concentration versus time curve was plotted in each instance and from this the following data have been determined: peak serum concentration (C_{max}), peak time (T_{max}), elimination half-life ($T_{1/2}$ of the terminal slope), and area under serum concentration/time curve extrapolated to infinity (AUC). These parameters for the 'high-dose' and 'low-dose' groups were compared statistically using Wilcoxon's rank sum test for unpaired samples.

RESULTS

The results are shown in Table I. There were marked inter-individual differences in prednisolone pharmacokinetics, but despite this there was no significant difference

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Table I. Patient details and pharmacokinetic parameters for prednisolone

Case	*Age* (years)	*Sex*	*Usual dose of prednisone* (mg/day)	C_{max} (ng/ml)	T_{max} (hours)	$T_{1/2}$ (hours)	*AUC* (hours/ng/ml)
1	43	F	20	170	1.5	3.5	862
2	35	M	15	280	0.5	3.8	1305
3	29	M	40	360	2.1	2.6	2529
4	22	F	20	300	1.0	4.1	1230
5	36	F	15	187	1.0	4.2	930
6	32	F	25	—	1.0	3.2	—
Mean ± s.d.	32.8 ± 7.1		22.5 ± 9.4	259 ± 80	1.2 ± 0.6	3.6 ± 0.6	1371 ± 674
7	53	M	2.5	254	0.5	4.3	1455
8	65	F	6	255	1.5	2.5	1945
9	51	M	5	193	1.0	5.7	997
10	51	M	5	163	1.5	3.7	1440
11	52	M	7.5	302	1.1	3.9	1572
12	48	M	10	212	1.5	3.1	1237
Mean ± s.d.	53.3 ± 6.0		6.0 ± 2.6	230 ± 50	1.2 ± 0.4	3.9 ± 1.1	1441 ± 319

between the mean values of any of the parameters for the two groups. Case 6 was found to have prednisolone in the base-line sample and therefore the peak concentration and the area under the curve could not be accurately determined.

Discussion

In this study, the pharmacokinetics of prednisolone in patients on low-dose maintenance steroid therapy for asthma did not differ significantly from those in patients requiring a higher dose. We conclude therefore that in these patients differences in serum prednisolone concentrations are not the major factor determining the dosage required to control asthma. Tanner et al. (1979) have shown that the amount of prednisolone bound to cortisol-binding globulin (CBG) remains constant over a wide dose range (10–200 mg) and that the percentage bound to albumin remains a constant percentage of the total remaining after CBG-bound prednisolone is removed. Thus protein binding changes and different amounts of 'free' prednisolone are also unlikely to account for differences in clinical effect. Other factors such as severity of asthma, tissue levels and target organ responsiveness may be more important.

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Short Communication

GENETIC BASIS OF SEX DIFFERENCES IN THE PREVALENCE OF ASTHMA

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Summary

The possibility that sex differences in the prevalence of asthma are caused by a genetic sex influence was investigated in 298 asthmatic patients with three or more positive skin tests (sex ratio = 1.35) and in 94 asthmatic patients with no positive skin tests (sex ratio = 0.58). The distribution of asthma among the male and female relatives of the male and female patients was uniform in both groups, indicating there was no genetic sex influence.

INTRODUCTION

It has long been known that the prevalence of atopic asthma is higher among males than females (Smith 1961), while the prevalence of non-atopic asthma is often higher among females than males (Molina et al. 1977). Although this dichotomy is not strict, the trend is of sufficient importance to warrant further investigation. In this paper, the possibility that these sex differences are caused by a genetic sex influence has been investigated.

Materials and Methods

Probands were selected from out-patients attending an asthma clinic at the Brompton Hospital during 1973–7. All patients had a history of episodic wheeziness and the majority demonstrated reversibility in airways obstruction either between successive visits or on treatment with a bronchodilator.

Skin prick tests to 21 common allergens were routinely performed on all patients. A positive reaction was defined as a weal with a diameter greater than that in the control test.

Information on first-degree relatives was obtained from a questionnaire completed by a physician on the patient's first visit to the clinic. The total number of first-degree relatives, the number with asthma and the sex of the relatives was recorded for each proband.

RESULTS

Among 469 patients attending the clinic, 298 had three or more positive skin prick tests and 94 had no positive tests. The sex ratio (males : females) was 1.35 in patients with three or more positive skin tests and 0.58 in patients with no positive reactions. In both groups, the prevalences of asthma did not differ between the male and female relatives of the male and female patients (Table I).

Table I. Prevalence of asthma among male and female relatives of male and female asthmatics

Probands	*Prevalence in relatives*		*Row significance*
	Male	Female	
With three or more positive prick tests			
Male ($n=171$)	49/464 (10.6%)	40/466 (8.6%)	$\chi^2=1.12$, $P>0.10$
Female ($n=127$)	30/388 (8.9%)	35/394 (8.9%)	$\chi^2=0$, $P=1.00$
Column significance	$\chi^2=0.46$, $P>0.10$	$\chi^2=0$, $P=1.00$	
With no positive prick tests			
Male ($n=35$)	4/96 (4.2%)	4/107 (3.7%)	$\chi^2=0$, $P=1.00$
Female ($n=59$)	9/169 (5.3%)	13/176 (7.4%)	$\chi^2=0.73$, $P>0.10$
Column significance	$\chi^2=0.32$, $P>0.10$	$\chi^2=1.55$, $P>0.10$	

Discussion

Under the hypothesis that asthma is genetically sex-influenced, the sex which is least often affected must inherit more predisposing genetic factors in order to manifest the disorder. The family history of asthma in affected members of this sex is increased correspondingly. Therefore, in atopic asthma where females are the sex least often affected, we would expect the prevalence of asthma to be higher in relatives of female asthmatics than in relatives of male asthmatics. This difference in prevalence should be most noticeable in female relatives; female relatives of female asthmatics should be more frequently affected than female relatives of male asthmatics. Conversely, in non-atopic asthma where males are the sex least often affected, we would expect male relatives of male asthmatics to be more frequently affected than male relatives of female asthmatics.

In the present study, there were no differences in the prevalence of asthma between the male and female relatives of males and females with either atopic or non-atopic asthma. This uniformity in the distribution of asthma shows that neither form of asthma is sex-influenced. Therefore the sex differences observed in many clinical populations must arise from factors other than those associated with the genetics of sex determination.

Acknowledgements

I would like to thank Professor M. Turner-Warwick and Dr J. Slack for their help in preparing this manuscript. The work was supported by the British Council.

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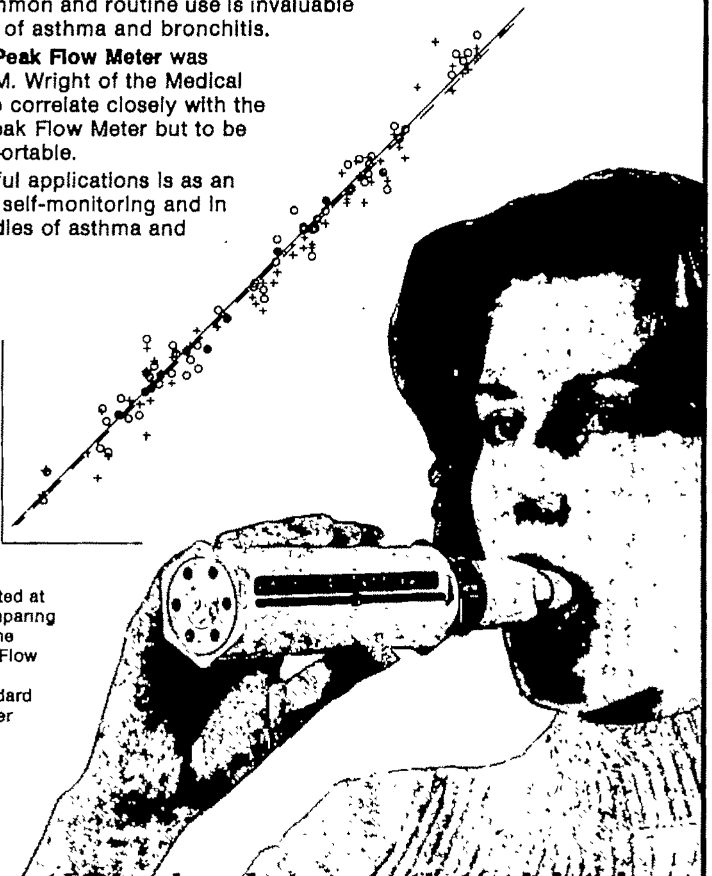

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Short Communication

PROPRANOLOL AND GIVING UP SMOKING

M. J. B. FAREBROTHER, SARAH J. PEARCE*, P. TURNER† AND D. R. APPLETON

Department of Medicine, St Thomas's Hospital Medical School, London; Chest Clinic, Newcastle Upon Tyne; and Department of Medical Statistics, University of Newcastle Upon Tyne

Summary

A placebo-controlled double-blind clinical trial was conducted to determine whether propranolol helps cigarette smokers to stop smoking; 73 subjects entered the trial but at the end of eight weeks only six had stopped smoking, three in the propranolol and three in the placebo group. There was no evidence of any helpful effect of propranolol in subjects trying to stop smoking.

INTRODUCTION

There is to date no effective pharmacological aid for cigarette smokers who wish to stop smoking (Royal College of Physicians 1977), except perhaps for the use of nicotine chewing gum (Russell et al. 1976), during which the possible harmful effects of nicotine continue. Propranolol is effective in relieving the somatic symptoms of anxiety (Leading Article 1976) and may help in the withdrawal of alcohol (Carlsson 1976), but earlier reports that propranolol was of help in opiate withdrawal have not been confirmed in double-blind studies (Resnick et al. 1976). We have conducted a placebo-controlled double-blind clinical trial to determine whether propranolol helps cigarette smokers to stop smoking.

Subjects and Methods

General practitioners were invited to refer cigarette smokers who wished to stop smoking and suitable subjects gave their informed consent. Subjects who were, or might be, pregnant and others in whom propranolol would be contraindicated were excluded (Visit 1). The subjects kept diary cards of daily cigarette consumption for 10 weeks. Treatment with propranolol 40 mg three times a day or matching placebo tablets administered double-blind was commenced at the beginning of the second week, but subjects were advised not to try to give up smoking at this stage because we wished to monitor any effect of the drug on pulse and blood pressure before cigarette consumption ceased. At the beginning of the third week (Visit 2) they were advised to try to stop smoking and were seen again at the end of the sixth week (Visit 3) and of the tenth week (Visit 4).

Seventy-three subjects entered the trial, 49 at the West Chest Clinic, Newcastle Upon Tyne, and 24 at St Thomas's Hospital, London. Details of the subjects in the propranolol and placebo groups are shown in Table I. Subjects completing each visit are shown in Table I. There was a high drop-out rate. The difference in attendance patterns between the propranolol and placebo groups was not significant ($\chi^2 = 3.94$ with 3 d.f.).

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Table I. Details of subjects and number of visits completed

	Propranolol	*Placebo*	*Total*
No. of subjects	35	38	73
Male	20	20	40
Female	15	18	33
Age (median and range)	39 (19–59)	36 (21–64)	
Cigarettes per day at entry (median and range)	31 (6–60)	28 (15–60)	
No. of visits completed:			
1	35	38	73
2	31	27	58
3	17	17	34
4	10	9	19

RESULTS

Of the 19 subjects at Visit 4, six had stopped smoking, three on propranolol and three on placebo. Another 10 of the 34 subjects who completed at least three visits had reduced their cigarette consumption by at least one half (for at least two weeks) by the time they left the trial. Five had received propranolol and five placebo.

DISCUSSION

This study failed to demonstrate any helpful effect of propranolol in subjects trying to stop smoking.

The drop-out rate was high and the number stopping in both propranolol and placebo groups was disappointingly small. Many of the subjects had already tried other methods to stop smoking and failed. Despite this the lack of difference between the propranolol and placebo groups suggests that any effect of propranolol which may have been missed because of the small numbers would be small and not clinically useful.

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We thank the Newcastle Chronic Bronchitis Survey (Dr A. G. Ogilvie, Dr C. Strang, Professor D. Newell, and Dr P. O. Leggat) for financial support; Imperial Chemical Industries Ltd, Pharmaceutical Division, for supplying the propranolol and placebo tablets; Miss E. Hutchinson and Miss M. Edwards for help in running the trial; and Miss Suzanne Cox for typing.

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BOOK REVIEWS

Lung Biology in Health and Disease, 1. Immunologic and Infectious Reactions in the Lung

Charles H. Kirkpatrick and Herbert Y. Reynolds

New York: Marcel Dekker. 1976. Pp. xviii + 595. Price SFr. 175

The purpose of this series is to provide an update for persons working in the respiratory field in its broadest sense and to communicate modern concepts in this rapidly expanding area. The first volume represents this approach well in what is fast emerging as an important and rapidly expanding area within the field of non-respiratory functions of the lung—that of defence against infection. Evolution of man has caused the lung to be one of the prime portals of entry of noxious material into the body and this book explores the various immunological components of the lung's defence mechanisms against invasion.

Each of its 24 chapters is written by a different author or authors and it is notable that for this task the editors have secured workers who are active in the field at present. The clarity and ease of reading varies enormously from chapter to chapter and many of its nearly 600 pages are heavy going. However, it is heavily referenced and enjoys the benefit of having been completed in about a year and therefore impressions of 'dating' are less than usual in books of this type in this fast-moving field. Most authors have reviewed the field, stressed new concepts and principles, proposed questions to be tackled experimentally and speculated as to the future sufficiently to whet one's appetite. However some chapters tend inevitably to raise more questions than they answer when attempting to reconcile conflicting results in a complicated field—and in this way the book may be confusing in places.

The volume is divided into three parts: description of the mechanisms themselves, description of the diseases which arise as a consequence of abnormally reacting defence mechanisms and description of the basis for (largely) immunological intervention to enhance waning defences in the treatment of lung disease.

Has the book achieved its purpose? It is probably too long and detailed to fulfil the role of useful review for the respiratory researcher outside this particular field, albeit a useful source of references. For the worker in the field it is dating rapidly, although of the selection of 'recent advances' books available it is the best. For a person entering the field as an active worker this book provides a useful concentrated review up to 1975. Finally, its cost is prohibitive to the individual, but the book should be part of every library with a significant section of respiratory medicine.

PETER COLE

Clinical Oncology

John Horton and George J. Hill

Philadelphia and London: W. B. Saunders. 1977. Pp. xvi + 819. Price £19.50

In developed countries malignant tumours are the second most common cause of death. All clinicians encounter their effects and are aware that changes are taking place in the understanding, diagnosis, assessment and treatment of cancer. It is increasingly evident that a satisfactory approach to the management of individual patients with cancer often requires the involvement of a surgeon, radiotherapist and medical oncologist from the beginning, in addition to the expertise of specialists in other disciplines. For those whose principal commitment is not to oncology there is a need for easily obtainable information in this rapidly changing field.

This book provides basic information across the whole range of clinical oncology. It is lucidly written by a strong team of contributors and the editors have achieved a reasonable uniformity of style with balance between the basic biological and pathological considerations and the accounts of tumours according to the region or tissue of origin. There are many useful references and helpful illustrations.

The chapter on intrathoracic cancers is sound but the specialists in this field will already be aware of most of the information therein. More could have been said about chemotherapy in bronchial carcinoma, especially oat cell tumours, where many would feel that potentially important advances have been made.

As an introduction to the subject and as a source of information about the spectrum of clinical oncology it is warmly recommended.

R. K. KNIGHT

Pulmonary Disease of the Fetus and Newborn

Emile Scarpelli, Peter M. A. Auld and Harold S. Goldman

Philadelphia: Lea & Febiger (London: Henry Kimpton). 1978. Pp. xviii + 680. Price £37.50

This volume gives an extensive review of the pulmonary system before, during and after birth. The wealth of information may be judged by the fact that there are over 1800 references. The quality of the many reproduced radiographs is excellent. Diagrams, traces, tables and graphs are of good size and clearly labelled. The volume is well indexed and the type clear.

The opening chapter has extensive and detailed methods of examination of the lungs, physiological, anatomical and clinical, starting with the assessment of pulmonary maturity in utero, progressing through all the facets of lung development and function to adulthood. Much useful information is given in anatomical drawings, tables of normal values, nomograms of respiratory function and acid–base parameters. The pathophysiology of the lungs is discussed and its effect on the blood-gas status described. This is followed by a historical review of cardiorespiratory resuscitation and mechanical ventilation, detailed descriptions being given of modern methods and equipment.

Pulmonary disorders, common and rare, which can be treated by surgery are described and the modern surgical techniques are discussed. The medical disorders of the lung include discussion of aetiology, cause and prognosis and modern management, especially of asthma and cystic fibrosis. The chapter on the latter condition is long, covering much of past and present research, and presents in some detail the non-pulmonary aspects of the disorder and their management.

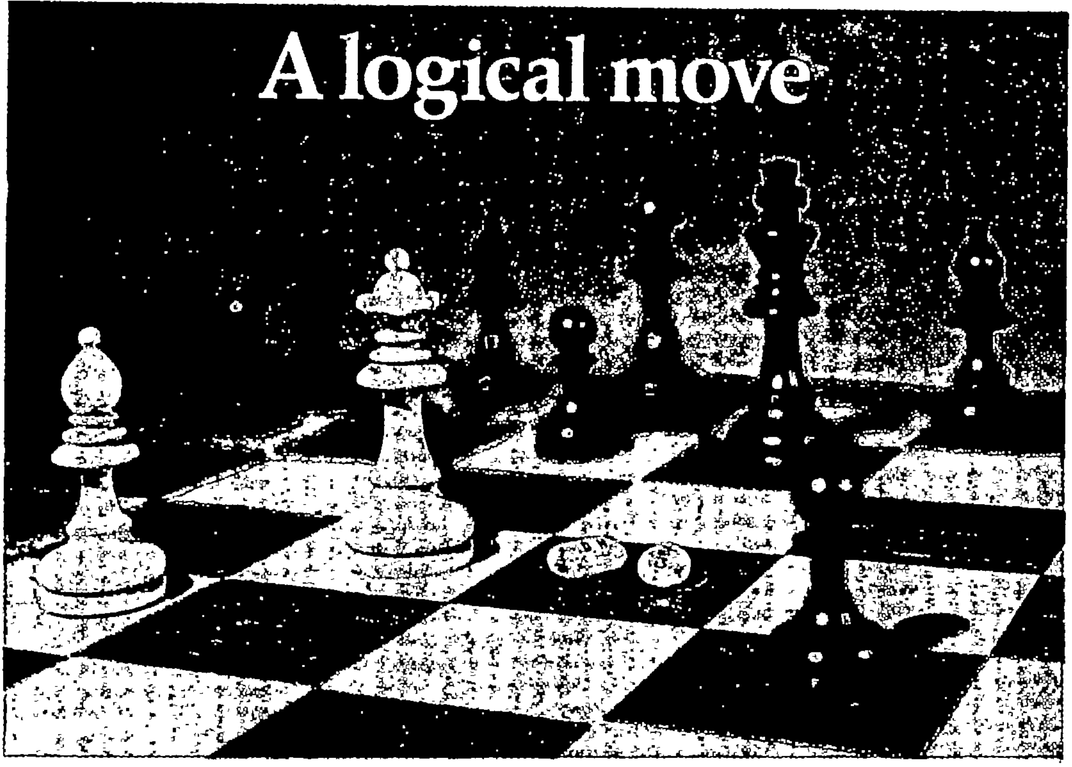
About one-fifth of the volume is devoted to the pulmonary disorders and care of the newborn and includes calorie and fluid requirements, maintenance of temperature control and haemostasis, techniques of monitoring and indications for the varying types of mechanical ventilation. These chapters make an excellent textbook for a neonatal unit.

There can be few disorders, even those with a remote effect on the lung, which are not mentioned in the volume. The chapter on extrapulmonary diseases, systemic disease and toxins includes useful details of management in poisoning by hydrocarbons and salicylates.

The final chapter discusses modern development in radiology in relation to paediatrics giving indications for the use of the new techniques. The radiographs used for illustration are well marked and labelled to define the abnormality present.

In a short review it is difficult to do justice to this unique volume. It will no doubt be a valued reference book for those interested in the lung in infancy and childhood and should find a places on the shelves of most medical libraries. The editors are to be congratulated that, with so many authors, there is so little repetition and that a balance has been maintained between the various disciplines.

MARGARET B. MEARNS



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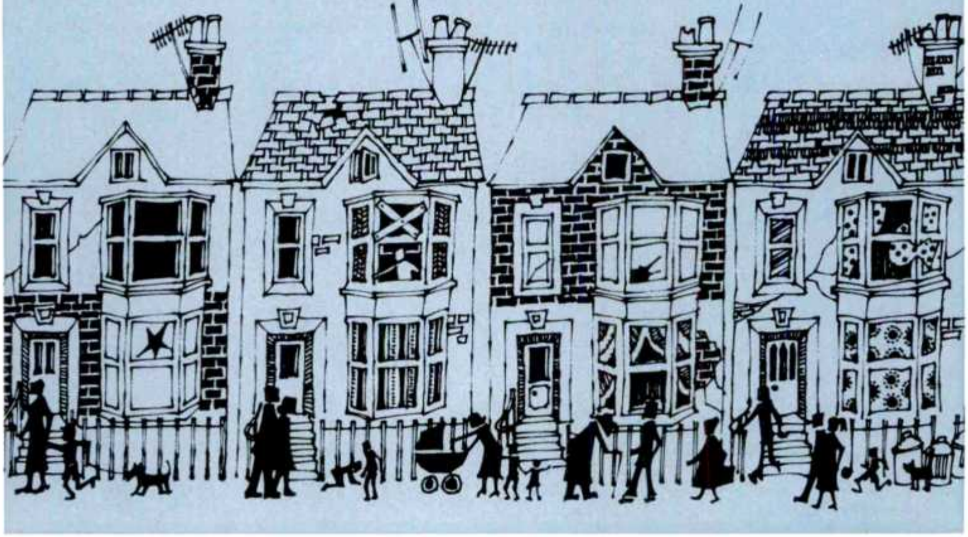

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Review Article

GASEOUS DIFFUSION IN THE LUNGS

Keith Horsfield

Midhurst Medical Research Institute, Midhurst, Sussex, England

The change in environment experienced by the vertebrates when they moved from the habitat of the sea to that of dry land brought with it some evolutionary changes in their respiratory mechanisms. Water can pass over the gills of a fish in a continuous flow bringing oxygen directly to them. In the land vertebrate, however, the need to conserve water which would be lost from an external gas exchange membrane has resulted in the development of an internal lung. The airways of mammals are a complex system of branching tubes open to the atmosphere at one end only and this necessitates reciprocating flow to achieve ventilation. But convective flow of inhaled fresh gas can not continue right up to the alveolar walls because these form blind endings in the airways. Some other mechanism must therefore move oxygen molecules up to the alveolar walls and carbon dioxide molecules away from them. This mechanism, by which gases in the respiratory airways become mixed, is molecular diffusion; without it mammalian lungs would be unable to exchange oxygen and carbon dioxide between air and blood.

Inspired oxygen moves down the airways to the blood by three distinct physical processes:

1. Convective flow in the conducting airways.
2. Molecular diffusion in the gas phase in the respiratory airways.
3. Molecular diffusion in the tissue phase across the alveolar–capillary membrane.

There is, of course, some overlap and interaction between (1) and (2), since diffusion also occurs in the conducting airways and convective flow in the respiratory airways. Each process, going down, is progressively less efficient at transporting gas, but this inefficiency is compensated for by the diminishing distance over which each operates and the rapid increase in the cross-sectional area of the airways distally, terminating in about 80 m^2 of alveolar surface area. These correlations between structure and function have been discussed in a previous article in this Journal (Horsfield 1974).

The purpose of this article is to review the role of molecular diffusion in the respiratory processes of normal lungs, how diseases affect it and how pulmonary function tests attempt to measure it. Complex mathematical equations have been deliberately avoided in order to make the text more easily understandable, but a few simple equations have been included. Those who are interested in this aspect should be able to find their way into the subject from the references.

MOLECULAR DIFFUSION

Molecules in a gas are in constant random motion, travelling in straight paths until colliding with other molecules or the walls of the container, when they bounce off in a new direction. If two species of molecules are introduced into a closed container they will intermix by virtue of this motion. The process is more rapid at higher temperatures, which increase molecular movement, and slower at higher pressures, when the molecules are more crowded.

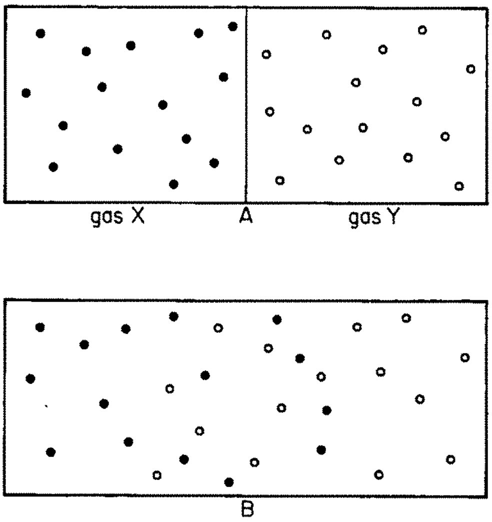

Fig. 1. Molecular diffusion in a cylinder. A, Two gas species separated by a partition. B, On removal of the partition the two gases start intermixing

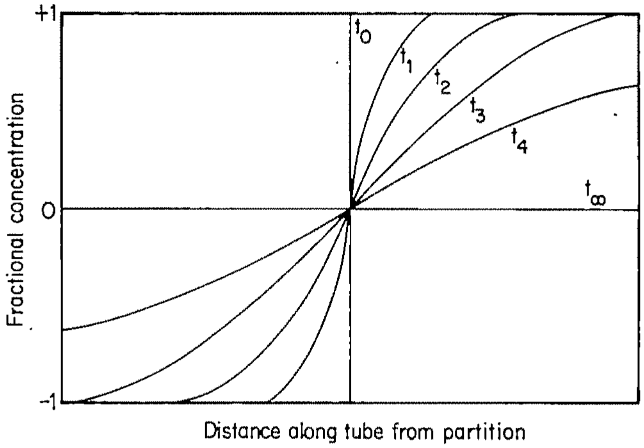

Fig. 2. Time course of diffusive mixing in the cylinder shown in Fig. 1. t_0 = time before removing partition, t_1 to t_4 = successive time intervals after removal of partition, t_∞ = infinite time (mixing complete)

Imagine a cylindrical container with a thin movable partition down the middle (Fig. 1A) and a different gas in each half. At time zero the partition is instantly removed and the two gases diffuse into each other (Fig. 1B). At first mixing is rapid but as each gas becomes more evenly distributed between the two halves the rate of mixing diminishes (Fig. 2). The quantity of gas passing across a plane of section in a given time is proportional to the concentration gradient, the cross-sectional area and the diffusivity of the gas. Diffusivity is expressed as the diffusion coefficient (D), the quantity of gas diffusing across unit area in unit time per unit gradient of concentration. This must be at a stated temperature and pressure. It has the basic units of $cm^2\ s^{-1}$ and is inversely proportional to the square root of the molecular weight of the gas, so that the larger the molecule the less easily it diffuses.

When two gases mix by diffusion the behaviour of each is modified by the nature of the other. Thus oxygen will diffuse into sulphur hexafluoride at a rate different from that at which it will diffuse into hydrogen.

The diffusion coefficient must therefore be stated for two gases, for example oxygen and nitrogen diffusing into each other at 20°C, $D = 0.22\ cm^2\ s^{-1}$; this is termed a binary diffusion coefficient. Table I gives the binary diffusion coefficients for some gases commonly used in respiratory work.

Table I. Binary diffusion coefficients (D) in cm^2/sec, at 37°C and 746 torr, dry

Gases	D	*Gases*	D
O_2 in N_2	0.256	He in N_2	0.743
CO_2 in N_2	0.181	He in CO_2	0.662
CO_2 in O_2	0.170	O_2 in He	0.893
CO in N_2	0.237	SF_6 in N_2	0.105
CO in O_2	0.247	SF_6 in O_2	0.099
CO in CO_2	0.179	SF_6 in CO_2	0.076

After Worth et al. (1978).

In Fick's first equation of diffusion the driving force is stated in terms of the concentration gradient

$$\frac{dQ}{dt} = -AD\frac{dc}{dx}$$

where Q is the quantity of gas, t is time, A is the area over which diffusion is occurring, c is the concentration of the gas species, D is the diffusion coefficient and x is linear distance.

The equation simply says that the rate at which a substance diffuses, dQ/dt, is proportional to the area, the diffusion coefficient and the concentration gradient, dc/dx. The minus sign indicates that the direction of movement is down the concentration gradient. With gases in the gas phase, partial pressure is proportional to concentration and in respiratory work it is common to think of diffusion in terms of partial pressure. Strictly speaking, however, it is the activity (fugacity) of the gas which drives diffusion, which is similar to but not quite the same as partial pressure.

When we come to consider diffusion in the blood and lung tissues another factor has to be taken into account, which is that the gas is soluble in serum and tissues. An example of the effect this has is as follows. Consider a two-phase system (Fig. 3) at 37°C with saline in one half equilibrated with oxygen at a partial pressure of 100 mmHg and olive oil in the other half equilibrated with oxygen at 40 mmHg, the two separated by a thin membrane. The concentration of oxygen is nearly twice as much in the oil, but oxygen will diffuse in the direction of the partial pressure gradient, that is against the concentration gradient, from the saline to the oil. In calculating the quantity of gas diffusing in a solvent, partial pressure must be used. If the solubility is α then concentration $c = \alpha P$, where P is the partial pressure, and Fick's equation becomes

$$\frac{dQ}{dt} = -AD\alpha\frac{dP}{dx}$$

where dP/dx is the partial pressure gradient.

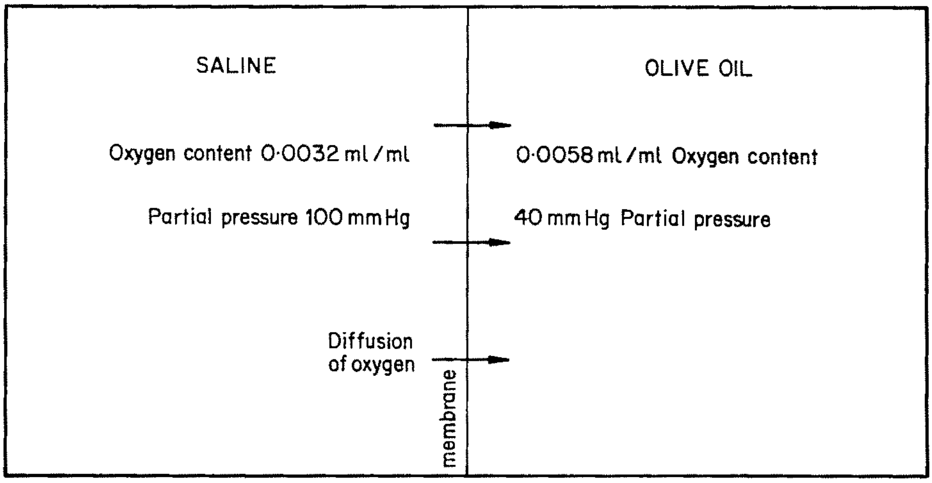
SALINE
OLIVE OIL
Oxygen content 0·0032 ml/ml
0·0058 ml/ml Oxygen content
Partial pressure 100 mmHg
40 mmHg Partial pressure
Diffusion of oxygen
membrane

Fig. 3. Diffusion of oxygen in a two-phase liquid system. Although the oxygen content of the olive oil is greater the direction of diffusion is down the partial pressure gradient. The difference in content is due to the greater solubility of oxygen in olive oil

TAYLOR DISPERSION

The interaction between convective flow and simultaneous molecular diffusion in the airways, though not clinically important, is of considerable interest. The phenomenon was first investigated by Taylor (1953). If a gas, such as nitrogen, flows down a long straight tube at a velocity appropriate for laminar flow a parabolic velocity profile develops (Fig. 4A). Gas at the centre of the tube flows fastest and that at the edges slowest, and when fully developed the gas at the centre moves at twice the average velocity. Suppose now that a different gas, such as oxygen, is introduced into one end of the tube, starting off with a perfectly straight front between the two (Fig. 4B). As the oxygen flows down the tube displacing the nitrogen in front of it, the parabolic velocity profile causes the oxygen molecules in the centre of the tube to move faster and hence to progress further down the tube. A parabolic *concentration* profile would develop (Fig. 4C) if no mixing occurred between the two gases. However, diffusive mixing does occur, blurring the interface and changing the shape of the concentration profile. Although gas molecules move in all directions, it is convenient to think in terms of two components of their movement, axially along the tube and radially across it. Thus oxygen diffuses radially out of the central core and into the surrounding nitrogen and nitrogen in the reverse direction (Fig. 4D). Those oxygen molecules which diffuse radially enter the slower-moving peripheral stream and are therefore transported more slowly than before. The higher the diffusion coefficient the more easily does radial diffusion occur, so that heavier gases tend to stay in the central core and be transported more rapidly.

Comparing two gases in a mixture, say the light gas helium (He) and the heavy gas sulphur hexafluoride (SF_6), in the circumstances just described, the front end of the concentration profile of the less diffusable gas SF_6 arrives first at a given station S in the tube (Fig. 5A). Up to the point where the two concentration profiles cross, more SF_6 than He passes S as the front flows through (Fig. 5B). Between this point and that where both gases reach maximum concentration, more He than SF_6 passes S (Fig. 5C). Finally the gases pass in equal quantities when the concentration profile has passed S.

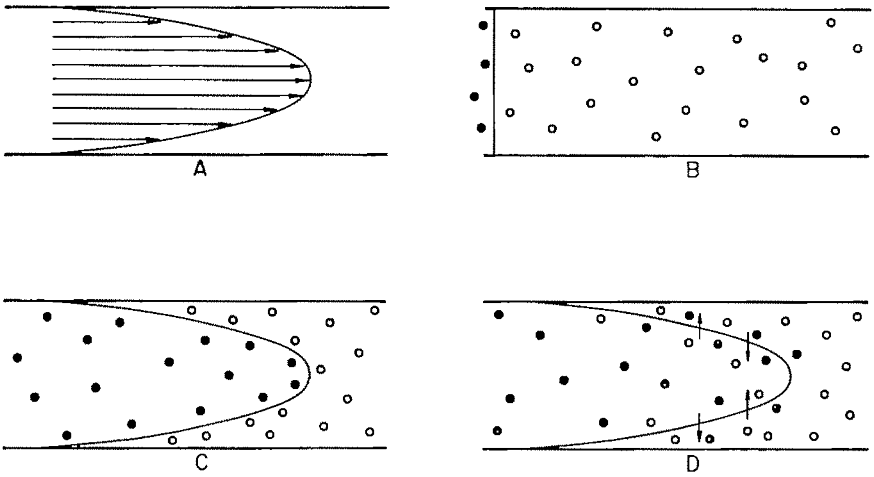

Fig. 4. Gas flow in a tube. A, Parabolic velocity profile when flow is laminar. B, A square wave of a second gas species is introduced. C, Parabolic concentration profile of the second gas. D, Radial diffusive mixing

The forward movement of a gas front undergoing Taylor dispersion is equivalent to an apparent diffusion with an 'apparent diffusion coefficient', k, where

$$k = D + \frac{r^2v^2}{192D}$$

and r = radius of tube, v = maximum velocity of flow in the centre of the tube and D = diffusion coefficient (Aris 1956). This apparent diffusion is with respect to a plane across the tube moving at the average flow velocity. Of the two terms on the right-hand side of the equation, D represents the ordinary diffusion coefficient in the axial direction, and $r^2v^2/192D$ represents the apparent diffusion coefficient due to Taylor dispersion. When D is very small compared with convective flow the concentration profile approximates to the parabolic form. If D increases relative to convection the second term becomes smaller and the concentration profile becomes shorter. When D is large relative to convection the second term becomes small, k approximates to D, forward flow is slow and axial diffusion predominates. Thus the concentration profile becomes flatter across the tube and the front lengthens. It can be seen that Taylor dispersion is maximally manifest in the intermediate situation. Furthermore, the value of the term $r^2v^2/192D$ is inversely proportional to D, a mathematical expression of what has already been described, namely that a heavier gas disperses longitudinally more than a lighter one.

It is obvious that Taylor dispersion, concerned as it is with the front between two fluids, can operate only while the front is passing down the tube. Once it has passed, as at station S in Fig. 5C, there can be no effect from this mechanism.

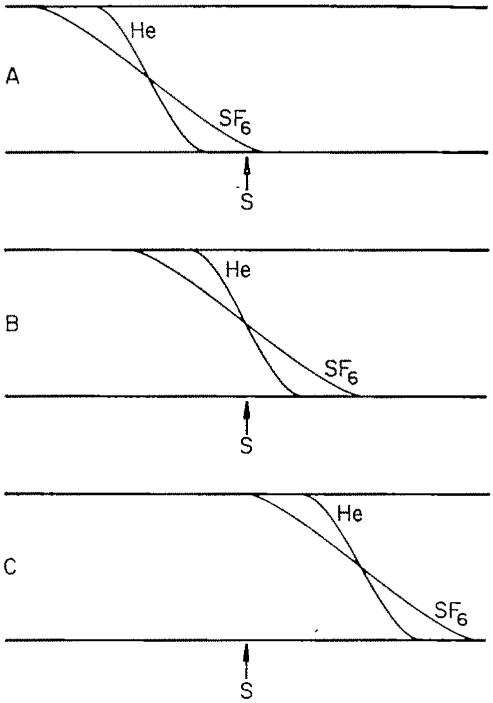

Fig. 5. Partial separation at the front of a mixture of He and SF_6 flowing in a tube. A, SF_6 arrives at station S first. B, After the cross-over point more He than SF_6 passes S. C, After the front has passed, both gases pass in equal concentrations

DIFFUSION IN THE CONDUCTING AIRWAYS

Although the main function of the conducting airways is transport of gas by convective flow, molecular diffusion nevertheless occurs in them. The part played by simple diffusion in the forward (axial) transport of gas is necessarily small, because the quantity transported depends on cross-sectional area, which is relatively small, and on time in the airways, which is short. However, it seems likely that Taylor dispersion can occur in the conducting airways, at least in some of them in appropriate circumstances.

In man at rest, breathing normally, tracheal flow is not high enough to cause turbulence, but turbulence does occur at the larynx and during inspiration this disturbed flow is carried down a few generations of airways, gradually dying out. Secondary vortices are generated at bifurcations (Schroter & Sudlow 1969) and eddy currents may also occur where the surface is not smooth or bends suddenly. Each of these will cause mixing of the gas front, tending to counteract Taylor dispersion.

At high flows the tracheal flow regimen may approach turbulence. In this case the velocity profile, and hence the concentration profile of a second gas, are both flat, minimizing Taylor dispersion. In addition to these causes of mixing, convective flow in the upper conducting airways is high relative to diffusion, so that Taylor dispersion is minimal. Wilson and Lin (1970) were of the opinion that it does not occur to a significant degree and could be neglected, while Kvale et al. (1975) thought that it should be taken into account.

Flow in the intermediate sized conducting airways is laminar, with flow velocities appropriate for Taylor dispersion to occur, but in exactly which airways depends on the diffusivity of the gas and the magnitude of the flow. Individual bronchi are too short to permit fully developed laminar flow with a parabolic profile, and this prevents Taylor dispersion from occurring maximally.

In the small conducting airways, and more especially in the respiratory airways, forward flow velocity becomes low and radial diffusion rapidly obliterates radial gradients in airways of small calibre. Axial diffusion comes to dominate the formation of the longitudinal concentration gradient and is indeed the most important mechanism for moving gas in this region of the airways.

The form of the concentration profile of a gas leaving an airway segment is at least partly determined by its form in the gas entering the segment. No mechanism has an isolated effect—the airways act sequentially in series so that at any point the end result is the sum of the effects of all the preceding airways.

From the above discussion it can be seen that anything which changes flow and diffusivity will affect the mechanism of Taylor dispersion. Thus on exercise, when flow is increased, the region where it is maximal will move further down the airways. Test gases with widely differing diffusion coefficients will undergo maximal Taylor dispersion in different airways and to different degrees. Gases of the same diffusivity but of different viscosity might also behave differently because their flow regimens will differ. Diffusivity is related to the pressure of a gas; it will therefore be increased at altitude and diminished in compression chambers and in divers.

The difficulty in calculating the effects of all these variables, and of defining detailed airway geometry, make it impossible at the present time to quantitate the effects of Taylor dispersion. In my opinion and that of Chang (1976) and Pack et al. (1977) it makes no significant contribution to normal respiration, but there is considerable evidence that it can be detected experimentally by using gases of widely differing diffusivity.

EXPERIMENTAL DEMONSTRATION OF TAYLOR DISPERSION

Van Liew and Mazzone (1977) showed how the longitudinal concentration profile of SF_6 flowing down a long straight tube is longer than the front of He, appearing in advance of the front of He but reaching full concentration later. A glass model of five generations of symmetrically branching tubes was used by Scherer et al. (1975) to demonstrate enhancement of the effective diffusivity of benzone vapour in the main stem. A hollow cast of the airways of a pig lung was used by Horsfield et al. (1977) to show that when a mixture of gases was blown down the main bronchus the front of SF_6 arrived distally in advance of that of either He or Argon (Ar). In dog lungs the transit time of carbon monoxide (CO) was observed by Wagner et al. (1969) to be less than half that expected for convective flow, a result they attributed to Taylor dispersion. Mazzone et al. (1976) found that He, when inhaled in a mixture of differing diffusivities, penetrated less deeply into the lung than expected, and this they attributed to radial diffusion of He. A similar result was obtained by Hogg et al. (1972). They showed that in dog lungs insufflated with beads SF_6 penetrated deeper than He, and this they attributed to Taylor dispersion.

A different kind of experiment has been to use gases of differing diffusivities to transport O_2 or CO into the lungs, and measure in some way their rate of arrival at the alveolar–capillary membrane. Johnson and Van Liew (1974) measured arterial blood Po$_2$ when O_2 was inspired in He and in N_2. They found Pao$_2$ rose more rapidly with the O_2/N_2 mixture. The uptake of CO, when inspired in He, N_2 or SF_6, plus O_2, was measured by Kvale et al. (1975). It was greatest in SF_6 and least in He. In both the above experiments the authors' interpretation was that the test gas is more effectively carried into the lung by the denser carrier gas which is more effectively dispersed longitudinally by Taylor dispersion.

Whether pathological changes affect gaseous diffusion or Taylor dispersion in the conducting airways is not known. There remains the possibility, as yet unexplored, that the pattern of Taylor dispersion in diseased lungs might be used as a test of function or of structural change.

TERNARY DIFFUSION

In respiratory experiments performed on living animals and man at least three gases are present in the lungs, and sometimes more. The presence of each gas affects the diffusion of the others and it is pertinent to enquire whether the binary diffusion coefficients commonly employed in calculations are adequate. If this problem is examined in detail it will be seen to be very complex indeed because during a respiratory manoeuvre the concentrations of the various gases at any point in the airways may change rapidly over a wide range. Worth et al. (1978) have determined diffusion coefficients for various gases in mixtures similar to alveolar gas. They found that the effective diffusion coefficients could be satisfactorily predicted by adding the reciprocals of the binary diffusion coefficients (diffusion resistances) weighted for the fractional concentration of the gases. The addition of more than one test gas, diffusing in the same or opposite directions, had no effect on diffusion provided that the concentrations were below 1%. At up to 10%, however, some interactions were observed. Water vapour was found to diminish D for light gases, have little effect with normal respiratory gases, and to increase D with heavy gases.

Modell and Farhi (1976) investigated ternary diffusion using He, O_2 and N_2. Starting with 21% O_2 in He at one end of a partitioned cylinder and 21% O_2 in N_2 at the other, when the central partition was removed the concentration of O_2 at the N_2 end fell, while it rose at the He end; it then returned to equilibrium concentrations. Between one and seven minutes in the experiment the concentration of oxygen mixing by ternary diffusion was actually increasing against a concentration gradient. The explanation for this is that He diffusing rapidly into the O_2/N_2 mixture caused the pressure to rise at that end of the cylinder, and hence produced convective flow in the direction of the O_2/He mixture. There was thus a nett movement of O_2 towards the He, producing an increase in O_2 concentration. Thus when non-respiratory gases are inhaled for the purpose of physiological investigation one cannot be certain that a gas in the airways is always moving in the direction of the concentration gradient. A degree of caution in the interpretation of such experiments is therefore required.

DIFFUSION IN THE AIRWAYS DISTAL TO THE TERMINAL BRONCHIOLES

Airways distal to the terminal bronchioles bear alveoli and are therefore termed respiratory, though Weibel (1963) termed the respiratory bronchioles transitional. Together the structures supplied by a terminal bronchiole constitute an acinus, which is usually pyramidal unless its shape is constrained by a pleural edge or a large adjacent structure. Both the airway and the artery enter at the apex. The airway then divides frequently so as to give throughout the lung a rapid increase in summed cross-sectional area, from about 80 cm^2 at the respiratory bronchioles to 10^4 cm^2 in the distal ducts, this occurring over a length of about 7 mm. Over 80% of the volume of a lung inflated to 75% of total lung capacity is made up of acinar air.

With such a large cross-sectional area available molecular diffusion inevitably plays an important part in the movement of gas molecules in the respiratory airways. Because of the small size and inaccessibility of the structures concerned, investigation of diffusion in situ is difficult. The main efforts directed at this problem have been of two kinds: (1) study of the behaviour of gases of different diffusivities when respired, and (2) mathematical analysis of more or less complex models.

Behaviour of gases diffusing in the respiratory airways

As has already been pointed out, oxygen is carried into the respiratory zone by convective flow and reaches distally-situated alveoli by molecular diffusion (Fig. 6). Similarly, carbon dioxide diffuses out in the reverse direction. There is thus a mixing of gases in the respiratory zone brought about by molecular diffusion, and this is the most important function of the airways at this level. It can be simply illustrated by the single breath test for nitrogen, in which a breath of 100% oxygen, usually 1000 ml, is inspired, and the concentration of nitrogen in the following expirate is measured and plotted against expired volume. If mixing within the respiratory airways were complete, but none at all occurred between the respiratory and the conducting airways, the expired nitrogen plot would be as in Fig. 7A, with no nitrogen in the first 150 ml or so, then a sudden upstroke in concentration, and finally a perfectly level plateau of alveolar nitrogen diluted with inspired oxygen. The 150 ml containing no nitrogen is the dead space, that is it represents that part of the airway in which no diffusive mixing has occurred (convective mixing on expiration being ignored). In reality the concentration curve is more sigmoid, with a less vertical upstroke and usually a gently rising plateau (Fig. 7B). The dead space can still be determined from this curve in terms of the volume of unmixed gas (Cumming et al. 1971) but the slope of the plateau has been the cause of much discussion. On the one hand it has been thought to represent regional variations in ventilation with oxygen, followed by regional variations in rates of emptying, known as regional inhomogeneity. On the other hand, it has been thought to represent a failure of complete diffusive mixing in the respiratory airways. More rationally, it can be considered as the result of the interaction between regional factors, both anatomical and functional, and molecular diffusion (Pack et al. 1977).

It is not the purpose of this paper to discuss the relative merits of these different interpretations, but rather to concentrate on the role of diffusive mixing.

If we consider the process of getting oxygen up to the alveolar capillary membrane and carbon dioxide away from it, and also the maintenance of a flux of these gases through the membrane, it is *a priori* obvious that concentration gradients for these gases must exist, otherwise there would be no driving force for diffusion. The question is, then, not whether there is a gradient but rather what is its magnitude?

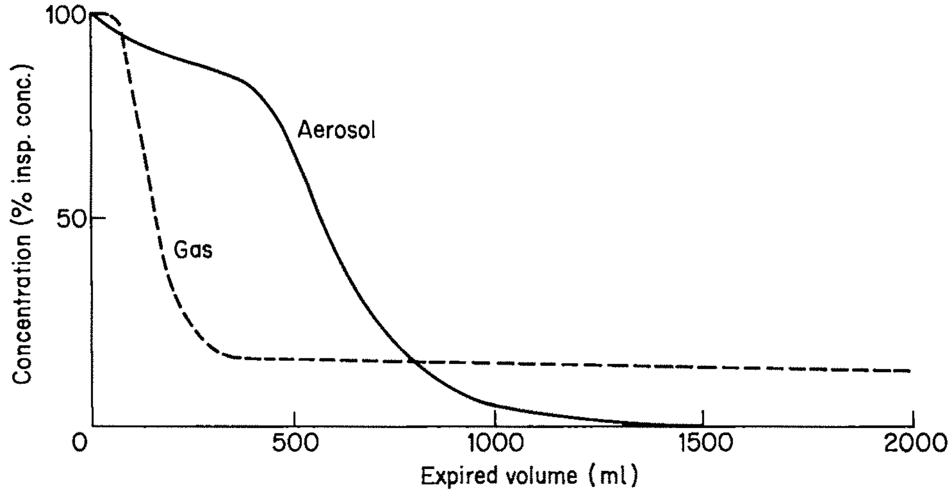

Fig. 6. Concentration–expired volume plots of a non-diffusing aerosol and an insoluble gas such as helium after inspiring 600 ml of each. None of the aerosol, which moves mainly by convective flow, has reached distally, whereas the He has mixed relatively well by molecular diffusion. The difference between the two curves illustrates the importance of diffusive mixing. (*From Muir 1966*)

Investigation of diffusive mixing has been carried out using gases each of different molecular weight, commonly helium, neon and sulphur hexafluoride. Thus if a mixture containing these gases is inspired and expired, then after the dead space the early part of the expirate contains more sulphur hexafluoride and the later part more helium, as shown in Fig. 8 (Georg et al. 1965; Cumming et al. 1967; Power 1969; Hogg et al. 1972; Sikand et al. 1976). Similar findings were obtained by Mazzone et al. (1976), except that in their experiments less helium than expected mixed peripherally, a result attributed to the effects of Taylor dispersion reducing its penetration. These demonstrations that the components of a gas mixture may partially separate in the airways cannot be explained simply by regional differences in ventilation since the gases were inhaled together; they must therefore result from molecular diffusion and possibly the interaction of diffusion with convection. A period of breath-holding between the inspiration of the gas mixture and its subsequent expiration results in a diminution of the concentration

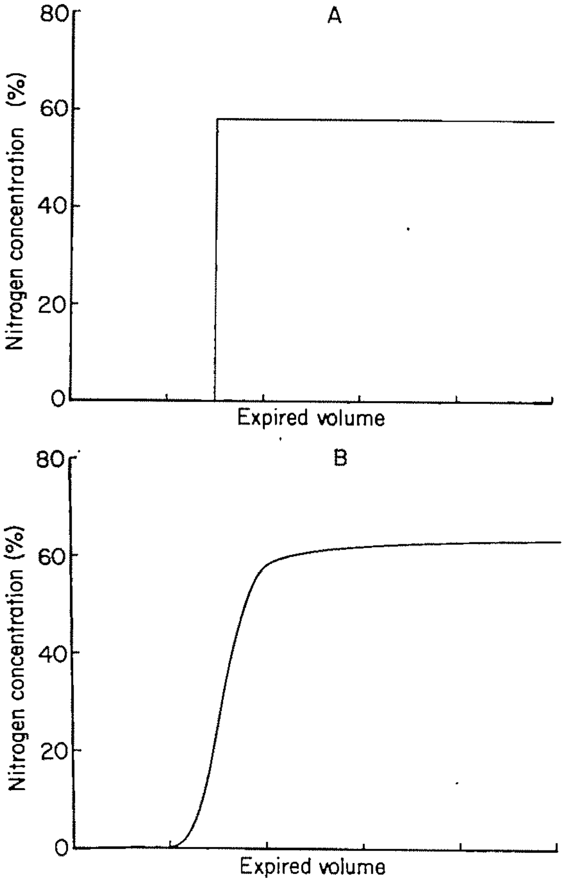

Fig. 7. Single-breath nitrogen test (see text). A, The theoretical square wave of nitrogen concentration which would result from perfect alveolar mixing and no conducting airway mixing. B, In reality alveolar mixing is imperfect (upsloping plateau) and mixing occurs in the conducting airways (sloping upstroke)

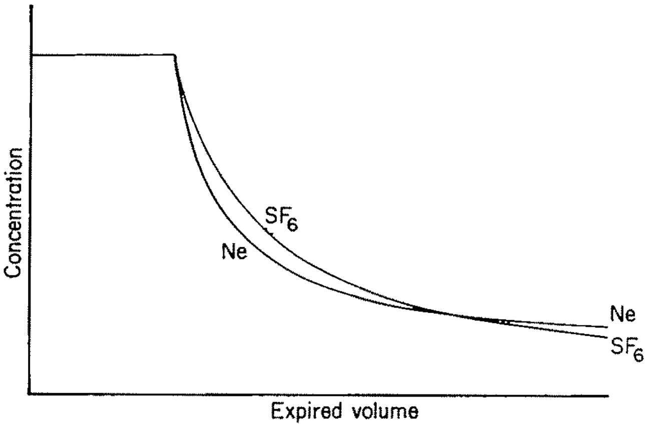

Fig. 8. The appearance of SF_6 and Ne in the expirate following inhalation of a mixture containing both gases

differences, the lapse of time permitting diffusive mixing to continue (possibly aided by cardiogenic mixing; see below).

Mathematical analysis of diffusion in the respiratory airways

The study of diffusion in the airways by model analysis was started by Rauwerda (1946) who, using a simple model of the acinus, came to the conclusion that diffusive mixing was so rapid that no measurable gradient would be left after one second. Since then a considerable number of model analyses have been reported. Each of these has concentrated on one or two particular aspects of the problem and produced various conclusions. Those which conclude that mixing is effectively complete within the time of a normal respiration include La Force and Lewis (1970) and Paiva (1973). Those which suggest that mixing is not complete include Cumming et al. (1966, 1971) and Pack et al. (1977). These authors also make the point that regional differences, convection and diffusion interact so that consideration of any one without the others is meaningless.

The variations of alveolar oxygen and carbon dioxide concentrations with time during the respiratory cycle have also been investigated using model analysis (Lin & Cumming 1973; Davidson & Fitz-Gerald 1974) as have the dead spaces for gases of different diffusivities (Cumming et al. 1971; Lacquet et al. 1975; Paiva et al. 1976; Sikand et al. 1976). Three good reviews of the general topic of model analysis of diffusion in the respiratory airways are those of Chang and Farhi (1973), Cumming (1974), and Pedley (1977).

Of critical importance in model analyses are the boundary conditions employed. In most of the studies so far discussed the assumption has been made that there is no concentration gradient ($dc/dx=0$) at the alveolar wall. Results from these studies suggest that gas mixing in the respiratory region is rapidly completed. Exceptions to this include Cumming et al. (1971), Butler (1974), Jones (1977), and Scrimshire et al. (1978), who assumed a no flux boundary condition at the alveolar wall. Their results suggest that gas mixing is incomplete. The problem of the correct choice of boundary condition is further discussed by Paiva et al. (1979) and is at present unresolved.

Gomez (1965) pointed out how the movement of gas molecules by convection falls off rapidly as they enter the respiratory zone in the lung while movement by molecular diffusion rapidly increases. There is thus a cross-over point where the two are equal (Fig. 9) at about the level of the terminal bronchioles. Cumming et al. (1971) investigated the possible effects of this by a model analysis in which both diffusion and convective flow were represented. They showed the presence of a static front of nitrogen at about 250 ml down the model of the airways, independent of the volume of oxygen inspired (Fig. 10); this occurs because at that point nitrogen is diffusing up the airways at exactly the same rate as it is being convected down. Using a more sophisticated analysis Paiva (1973) came to the same general conclusion.

Explanation of the static front

For a static concentration front to become established between a gas flowing down a tube and one diffusing up in the opposite direction the tube must have a trumpet-like shape. This the airways have if the cross-sectional areas at any given level are added together (Horsfield 1974). If oxygen, for example, is blown down the narrow end of such a tube into an atmosphere of nitrogen (Fig. 11) then nitrogen will diffuse up the wide end. Somewhere in the tube (flow and diffusivity being appropriate) a static nitrogen front develops. Some molecules (Fig. 11A), moving faster than average, will be further up the tube, but the further they get the higher is the velocity tending to sweep them down again. Other molecules (Fig. 11B), moving up the tube more slowly than average, will tend to be swept down, but the further down they go the slower is the velocity so that diffusion brings them back again. Although the nitrogen front is static oxygen continues to pass through it and out at the far end because there is a continuous flow of oxygen. In the lungs, where there is a closed elastic bag (the alveoli) distal to the tube, the absolute concentration of nitrogen continues to fall during inspiration as it is diluted by the incoming oxygen, but the position of the front is nevertheless static if flow is constant (Fig. 12).

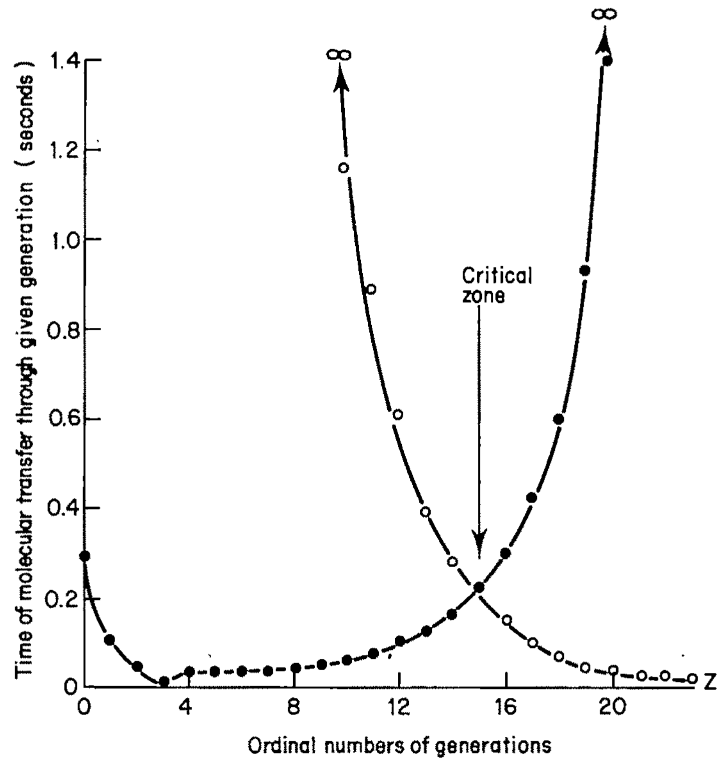

Fig. 9. The relative velocity of molecular transfer in the airways by convective (bulk) flow and molecular diffusion (see text). (*From Muir 1966*)

Paiva et al. (1976) developed a simple mathematical relation between anatomy (the shape of the trumpet), diffusivity, and flow. Where the front is static

$$\frac{\mathrm{dA}}{\mathrm{dx}} = \frac{\dot{V}}{D}$$

where A = summed cross-sectional area, x = linear distance, $\dot{V}$ = flow, and D = diffusion coefficient. In words, at the static point the rate of change of cross-sectional area with distance down the airways is equal to the flow divided by the diffusion coefficient. Thus, if the anatomy is known a plot of cross-sectional area against length can be drawn (Fig. 13) and a line of slope $\dot{V}/D$ constructed as a tangent to the graph. The point where the tangent meets the curve corresponds to the static point, which can be read off the abscissa in terms of length down the airways. When the calculations are made with values of D corresponding to hydrogen and sulphur hexafluoride, the static hydrogen front becomes established nearer the mouth than does the sulphur hexafluoride front, and thus the more diffusable gas has the lower dead space.

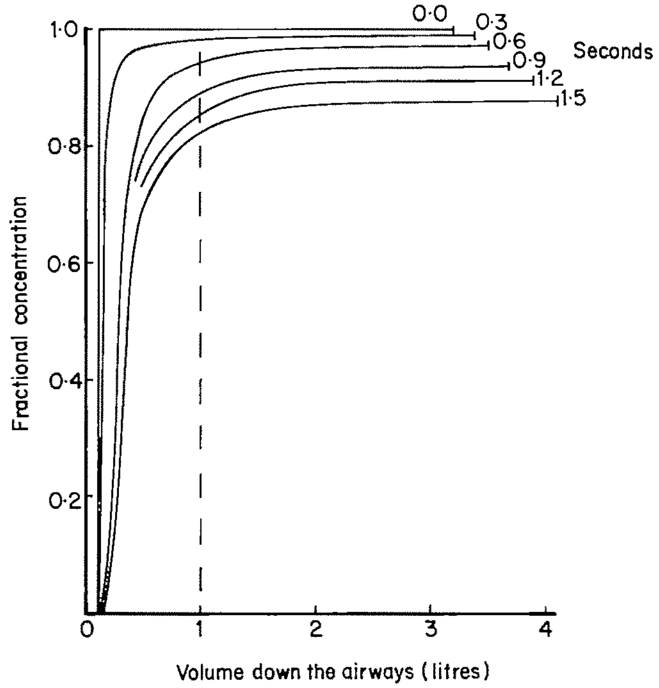

Fig. 10. Calculated nitrogen concentration profiles in a lung model during the inspiration of 1 litre of oxygen over 1.5 seconds. Note the static front at about 250 ml

The static front has been demonstrated in the airways of dogs by Engel et al. (1973) and Fukuchi et al. (1976). They also showed that in the living animal the position of the front oscillates back and forth with the heart beat and that this motion facilitates mixing between the gases on each side of it. Their data suggest that the effect of the heart beat on mixing is equivalent to increasing the diffusion coefficient within the airway by a factor of five.

Tests of mixing

The position of the concentration front is obviously one factor determining the magnitude of the 'anatomical' or 'series' dead space, which varies with lung volume (airway cross-section), the diffusion coefficient of the gas used, and the duration of any breath-holding period during which the interface will move up the airways by diffusion. The single-breath nitrogen test thus gives information on gas mixing with regard to both the slope of the plateau and the size of the dead space.

The multi-breath test is carried out by the subject inhaling a gas containing no nitrogen, breathing normally for several minutes. A mixture of 79% argon and 21% oxygen is suitable for this, avoiding the effects on ventilation which occur when 100% oxygen is used. Nitrogen is progressively washed out of the lungs and its end expiratory concentration measured. Plotting concentration on a logarithmic scale against breath number gives a curve which in a perfect mixing system would be linear, in a normal lung is slightly curved, and in an abnormal lung is more or less markedly curved (Becklake 1952). This technique has been improved by Prowse and Cumming (1973) who measured the quantity of nitrogen remaining in the lung after each breath and plotted nitrogen decay curves (Fig. 14). The degree of divergence from perfect mixing is expressed as an inefficiency, which contains both regional and series mixing defects. Such inefficiencies are seen in airway obstruction of all kinds, since in these inspired gas cannot mix well with alveolar gas. In centrilobular emphysema the dilatation on the respiratory bronchioles forms a series mixing chamber (Fig. 15A) which impairs mixing between inspired

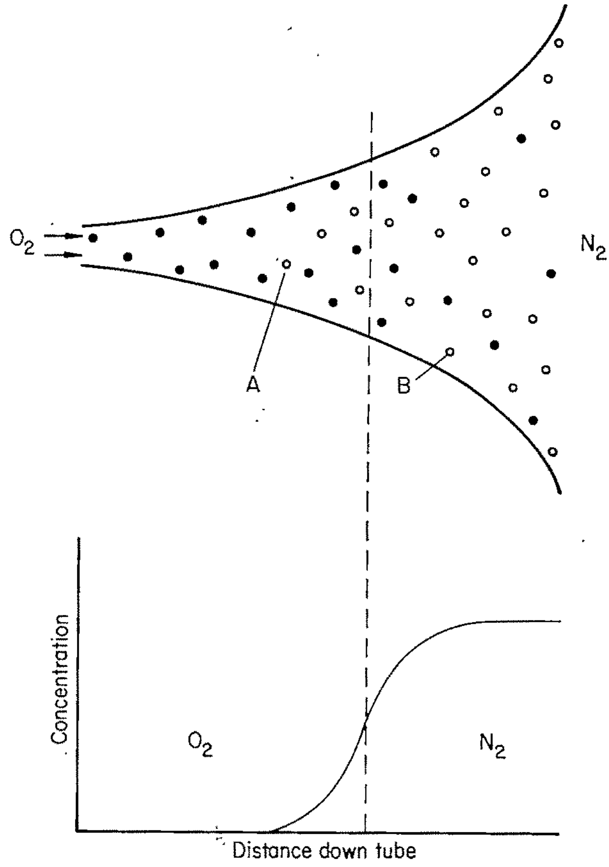

Fig. 11. Static front of nitrogen in a trumpet-shaped tube when oxygen is blown down at a constant flow. A, Molecules of N_2 diffusing up quicker than average. B, Molecules of N_2 diffusing up slower than average (see text)

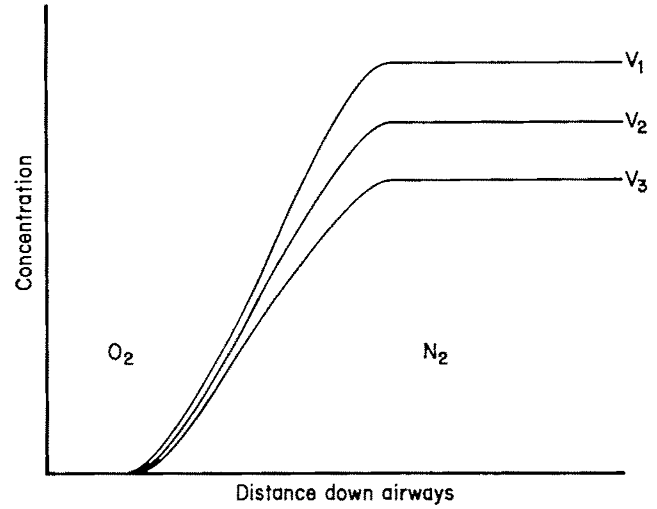

Fig. 12. Behaviour of static front in lung when flow is constant but inspired volume (V) increases. $V_3 > V_2 > V_1$

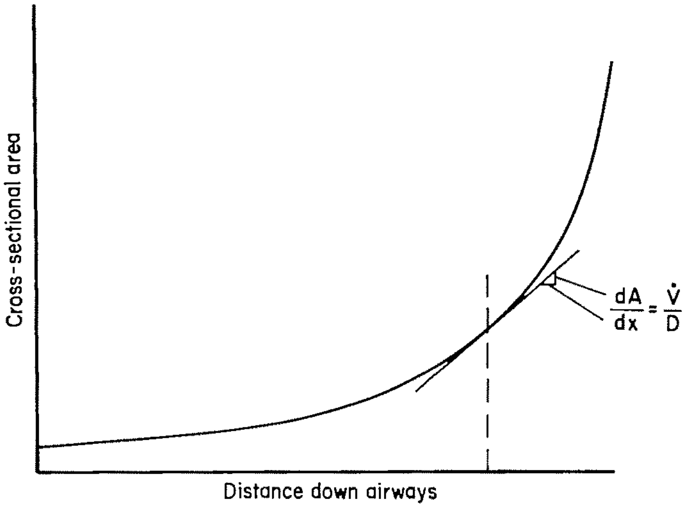

Fig. 13. Definition of the anatomical site of the static front. The curve is a plot of summed cross-sectional area of the airways at any given level against distance down the airways to that level. If flow ($\dot{V}$) and diffusion coefficient (*D*) are known, then the slope of the tangent dA/dx can be found. The point where the tangent touches the curve is the site of the static interface

and alveolar gas (Horsfield et al. 1973), while in panacinar emphysema mixing is slow in the distal dilatation (Fig. 15B). A series mixing problem of a different kind arises with blockage of peripheral airways with plugs of mucus, as in asthma. Collateral ventilation from adjacent acini can occur, but with a marked defect in mixing between the two (Fig. 15C).

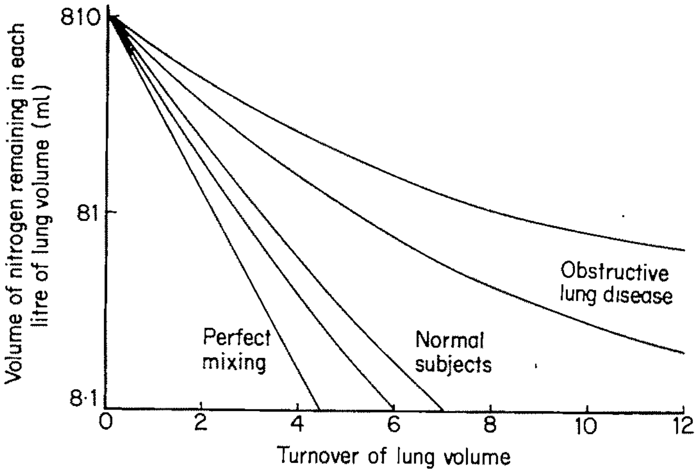

Fig. 14. Lung nitrogen decay curves obtained by breathing a mixture of 79% Ar and 21% O_2. One turnover of lung volume is when the sum of the tidal volumes equals the lung volume

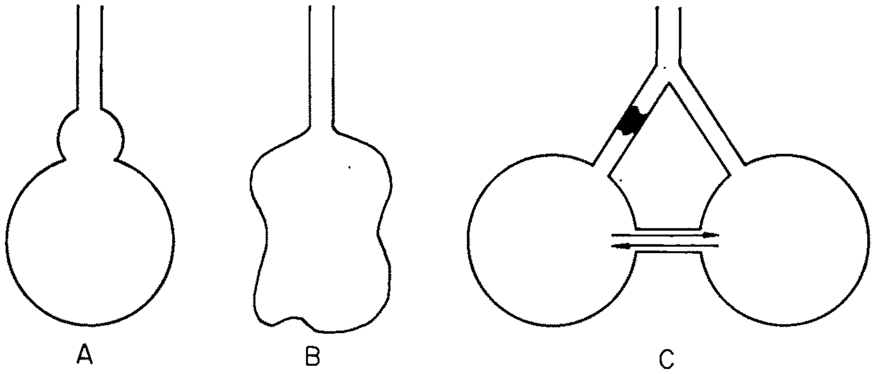

Fig. 15. Some lesions in airway disease causing serious mixing defects. A, Centrilobular emphysema. B, Panacinar emphysema. C, Airway blockage (asthma) with collateral ventilation of adjacent acini

DIFFUSION ACROSS THE ALVEOLAR–CAPILLARY MEMBRANE

Anatomy

The last part of the pathway taken by an oxygen molecule on its way to a red cell is the shortest but also the most complex—its passage through the alveolar wall. Four different tissues must be traversed before it reaches a haemoglobin molecule with which to combine (Weibel 1970/71). These are:

1. The surfactant layer.
2. The tissues of the alveolar wall.
3. The plasma in the capillary.
4. The red cell wall.

The surface layer of surfactant is 5–20 nm thick; it consists of a basal layer and a phospholipid film 2–3 nm thick. It fills out crevices and acute angles, where it may be 1–3 μm thick, thereby making the alveolar air space smoother and more rounded.

Tissues of the alveolar–capillary membrane are basically two cells thick, the alveolar epithelial cell and the capillary endothelial cell, each with its basement membrane (Fig. 16). Thus an oxygen molecule must traverse the cell membrane, cytoplasm, cell membrane and basement membrane of the epithelial cell, the interstitial space, and the basement membrane, cell membrane, cytoplasm, and cell membrane of the endothelial cell. This is the minimum. But the interstitial space between the two basement membranes may contain ground substance, fibrous tissue, or liquid. Although the cytoplasmic extensions of the cells occupy most of the alveolar surface area, the cells do have nuclei, and where interstitium or nuclei are present the thickness may be 5 μm or more.

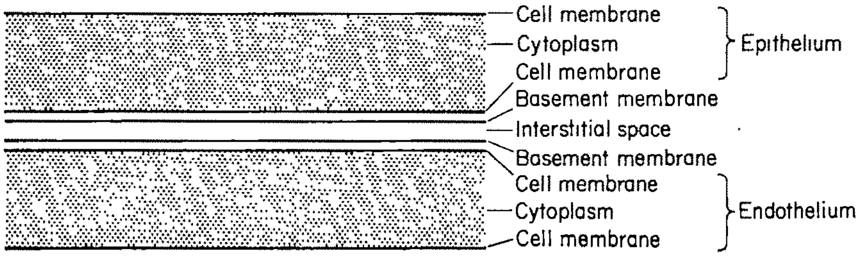

Fig. 16. Basic structure of the alveolar–capillary membrane

The plasma layer may be extremely thin, 5–10 nm, where the edge of a red cell appears to be in contact with the capillary wall, but in the centre of the capillary lumen oxygen may have to traverse half the capillary lumen in serum.

Diffusion of oxygen into the red cell and its reaction kinetics with haemoglobin is a separate subject and will not be dealt with here.

In a fully inflated lung the alveolar walls are probably flat, but at lower volumes the capillaries may bulge into the alveolar lumen. While the capillaries do not occupy the whole of the alveolar wall surface, if they are bulging into the lumen their surface area may not be much less than this. The red cells within the pulmonary capillaries have a total surface area which matches that of the alveoli, about 80 m^2.

Diffusion in tissues

When calculating the diffusion of gases through these structures the solubility of the gas in each is important. Table II (Weibel 1970/71) gives the diffusion coefficient, solubility, and permeation coefficient for oxygen in nitrogen, lung tissue, and plasma. Values for the surfactant layer are not known. Lung tissue and plasma are seen to have similar values which are markedly less than those for a gaseous medium.

Ternary membrane diffusion

By the use of analytical methods Chang et al. (1975) showed that ternary mixtures diffusing across a membrane may behave in unexpected ways. Thus there may be no diffusion across the membrane in the presence of a partial pressure gradient, or transfer

Table II. Solubility constant (α), diffusion coefficient (D), and permeation constant (K), where $K = \alpha D$, for oxygen in the lungs

Coefficient	*in N_2*	*in lung tissue*	*in plasma*
α	—	2.37×10^{-5}	2.8×10^{-5} ml/ml/mmHg
D	0.256	1.38×10^{-4}	11.5×10^{-4} cm^2/sec
K	—	3.3×10^{-8}	3.2×10^{-8} ml/ml/min/mmHg

where there is no gradient at all. The relevance of these findings to gas transfer in the lung is as yet unknown.

Factors affecting alveolar–capillary membrane diffusion

For transfer across the membrane to occur, an oxygen molecule must first reach the alveolar wall, then go into solution in the tissues, diffuse through them, finally to combine with haemoglobin. This process can be affected by various factors. Exudate, oedema fluid or excess surfactant within the alveolar lumen will greatly slow down the rate of arrival of oxygen molecules at the alveolar wall. The alveolar epithelial cells or the capillary endothelial cells may be thickened, and between them fibrous tissue may increase or fluid accumulate. Within the capillary the diffusion distance may be increased with capillary dilatation. The total functional surface area puts an upper limit on the transfer of gases; it is that surface area which is ventilated with fresh gas and in contact with functioning capillaries. Exercise causes capillary recruitment as pulmonary blood flow increases and this helps to increase oxygen uptake. Surface area varies with lung size, increasing during growth and varying over a wide range between individuals. It increases with inspiration and is reduced in such conditions as emphysema, embolism and pneumonectomy.

Tests of alveolar–capillary membrane diffusion

Diffusion across the alveolar–capillary membrane is usually estimated using carbon monoxide (CO). The method involves the inhalation of a small amount of CO, estimating its alveolar concentration, and calculating how much is taken up by the blood in a given time. From this the transfer factor for the lung for CO is calculated, usually as ml of CO per minute for each mmHg partial pressure difference. Capillary partial pressure of CO is taken to be zero because it combines so rapidly with haemoglobin. Hence the partial pressure difference is equal to the alveolar pressure. The test can be performed as a single breath with 10 seconds' breath-holding, or as a multi-breath method.

Because CO molecules have to traverse the total pathway already described, their rate of uptake is limited by the series resistances offered by the conducting airways, diffusive mixing in the respiratory airways, diffusion across the membrane, plasma and red cell wall, and the reaction kinetics with haemoglobin. The result obtained from an estimation of T_{LCO} is therefore dependent also on factors other than the alveolar–capillary membrane resistance, for example, on the imperfection of alveolar mixing. As we have already seen, this is probably the case even in normal lungs and is certainly the case in diseased lungs. Distribution of ventilation and perfusion may be mismatched so that CO going to unperfused areas will not be transferred to the blood. In such cases a low T_{LCO}, while measuring the ability of the lung to take up CO, is not necessarily a measure of the conductance of the alveolar–capillary membrane.

The other important determinant of CO uptake is the blood itself. Even static red cells in the pulmonary capillaries will take up CO, and so long as the quantity of CO is small enough the blood may not be a limiting factor. The number of red cells in the capillaries and their haemoglobin content are important, so that T_{LCO} may be increased in polycythaemia and decreased in anaemia. The longer the time spent in a capillary by a red cell the more likely is it to become a limiting factor, and conversely faster flow may increase uptake. Finally, the balance between the formation of carboxyhaemoglobin and oxyhaemoglobin determine how much CO is actually taken up by the haemoglobin, and this is affected by the partial pressures of CO, oxygen, and carbon dioxide prevailing in the pulmonary capillaries, as well as pH, temperature, and red cell chemistry. In spite of the above problems the measurement of T_{LCO} helps in the study of diseases affecting the alveolar wall. The significance of an abnormal result can be better interpreted from the above discussion.

IN CONCLUSION

Molecular diffusion is an important mechanism during all phases of the movement of gas from the external air to the red cells. It is difficult to study in intact animals and difficult to model mathematically. Results of new model analyses, each more complex and comprehensive than the last, regularly appear in the literature; whether the results will be worth the effort expended in obtaining them remains to be seen. No better illustration of the interdependence of physiology, anatomy and basic sciences can be found than in the study of molecular diffusion in the lungs.

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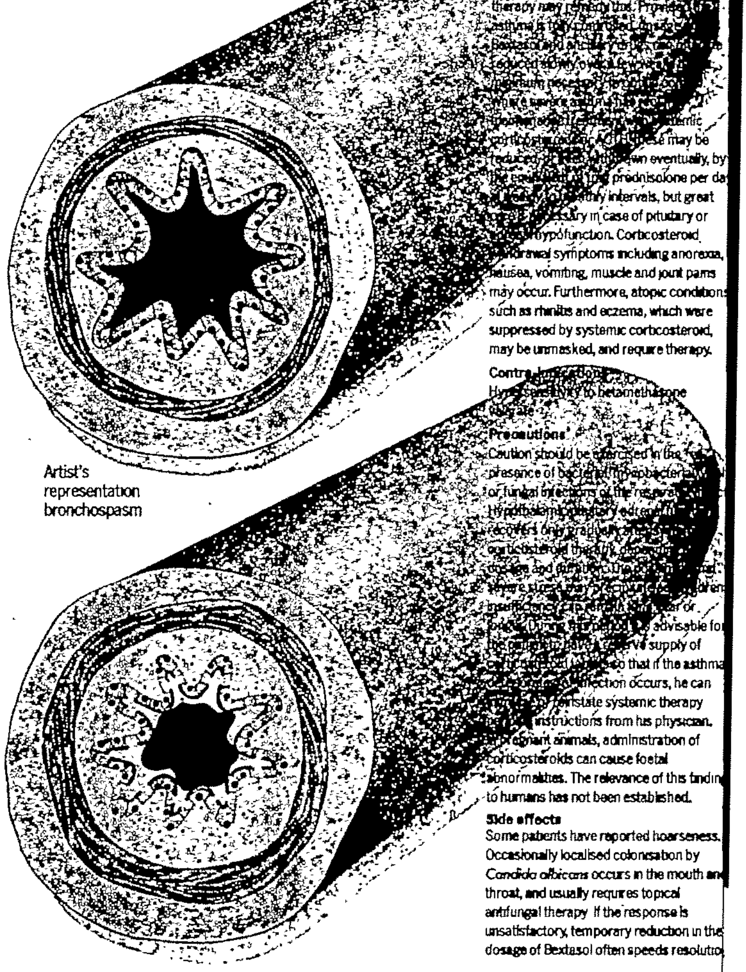

Artist's representation bronchospasm

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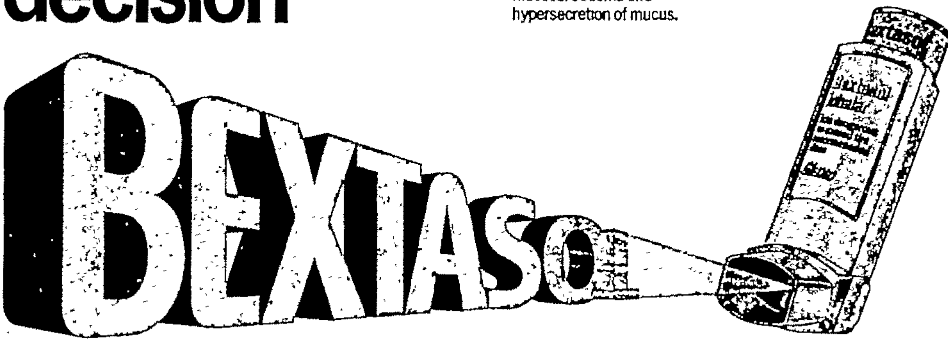

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A STUDY OF LIVE INFLUENZA VIRUS VACCINE IN PATIENTS WITH CHRONIC BRONCHITIS

Report to Medical Research Council's Committee on Influenza and Other Respiratory Virus Vaccines

Advisory Group on Pulmonary Function Tests in Relation to Live Influenza Virus Vaccines*

Summary

A multicentre study of the effects of influenza virus RIT 4050 (H3N2) in patients with chronic bronchitis was conducted by members of an MRC Committee. The results showed that RIT 4050 vaccine virus did not cause a deterioration in clinical or physiological status in these patients within the limitation of the relatively reproducible ventilatory tests which were employed. This conclusion applied equally to those who were inoculated and became infected and to those who failed to develop serological evidence of infection. The relatively high proportion of antibody-negative volunteers not infected by the inoculated virus raises doubts concerning the value of this method of immunization for patients at risk during influenza epidemics.

Introduction

A working group of clinicians and virologists was established in November 1975 under the auspices of the MRC Committee on Influenza and other Respiratory Virus Vaccines. The Group undertook to conduct studies on the possible clinical effects of live attenuated influenza virus, when used as a vaccine in persons with chronic lung disease, largely because of the conflicting results reported in the literature. Thus, Hall et al. (1976) found no adverse effects on pulmonary function following intranasal inoculation of an attenuated influenza virus into healthy adult volunteers, but Rosenzweig et al. (1975) reported decreased airflow in healthy persons inoculated with a different attenuated influenza virus. Prevost et al. (1975), using an attenuated intranasal virus vaccine in patients with chronic bronchitis, found no harmful clinical effects, but Zeck et al. (1976) found a small decrease in the forced expiratory volume (FEV_1) in some patients with chronic lung disease given a similar vaccine. Members of the working group had previously established methods suitable for the assessment of pulmonary function, using WRL 105 (H3N2) virus in mostly healthy volunteers, and later in geriatric patients and

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*Members of the group were: Professor Sir Charles Stuart-Harris (*Chairman*), Professor R. B. Heath, Professor C. W. Potter (*Secretary*), A. S. Beare, J. Collins, G. Cumming, W. N. Dunnet, D. W. Empey, P. Howard, K. G. Nicholson, P. D. Oldham, N. B. Pride, G. C. Schild and M. Sibellas; with the assistance of: M. J. Campbell, I. Gregg and M. Hardman.

others with chronic bronchitis; no significant changes were observed in the peak flow rate (PEFR) and FEV_1 of the several groups of persons during the period up to seven days after virus inoculation (Nicholson et al. 1976).

In a further study, tests were carried out with influenza virus strain 4A2, which possessed surface antigens derived from the A/Victoria (H3 N2) virus, in patients with chronic bronchitis; this virus had been shown to be attenuated for normal volunteers in studies at the MRC Common Cold Research Unit. However, strain 4A2 caused adverse clinical effects in 19 patients with chronic bronchitis and obstructive airways disease, including enhanced symptoms and deterioration in ventilatory function (Winson et al. 1977), and was later found to cause changes in pulmonary function of normal subjects. In addition, these studies also showed that the pulmonary function of patients with chronic bronchitis given live influenza virus might deteriorate at a date later than the period in which virus infection was detectable. From these results it was concluded that each life influenza virus vaccine must be assessed in patients with chronic bronchitis separately and specifically, since data from studies in normal subjects were not appropriate. To this end, the working party agreed to carry out a study in patients with chronic bronchitis of a further attenuated virus strain which was being developed for use in man.

Patients and Methods

Virus

The RIT 4050 (H3N2) virus strain, which has the surface antigens of the A/Victoria/75 virus, was provided as a lyophilised preparation by Dr A. Huygelen of the Recherche et Industrie Therapeutiques, Rixensart, Belgium. After reconstitution, it was given by intranasal drops at a dosage of $10^{7.05}$ 50% Egg Infectious Doses (EID_{50}) in a 0.5 ml volume. A placebo preparation without virus was used in parallel control studies, and the allocation of vaccine or placebo was made randomly; the clinician was unaware of the nature of the inoculum.

Patients

Only patients with chronic bronchitis and airways obstruction with an FEV_1 of >1 litre, no symptoms of cardiac disease and not under treatment with steroids being included; 86 patients with an age range of 28–78 years took part in the trial, the largest number being studied by K. G. Nicholson of the Clinical Research Centre, Northwick Park, in collaboration with Ian Gregg of the Group Practice, Kingston upon Thames. All the patients conformed to the accepted diagnosis based on the MRC Committee's definition of chronic bronchitis.

Symptoms. Because of the chronic symptoms of these patients, daily records were kept on a modified version of the self-recorded diary sheet employed by Lawther et al. (1970) who used the method to correlate symptoms with changes in air pollution. Patients were asked to tick in the boxes provided the daily experience of upper respiratory or systemic symptoms, and also to indicate whether lower respiratory symptoms (cough, sputum, difficult breathing or wheezing) were more (worse) or less (better) each day compared with the previous day. Some doubts existed concerning the interpretation of the daily comparisons, but workable records were obtained for symptoms following virus inoculation on seven days for each of 73 patients.

Pulmonary function tests. Spirometry and maximum expiratory flow volume curves (MEFV) were recorded on at least five occasions for each volunteer; these were done 7 and 21 days before inoculation, immediately before inoculation and two occasions in the three weeks following virus infection, usually days seven and 21. The flow rates of 50% and 75% on the expired vital capacity (V_{50} and V_{75}), and peak flow rates were read from the curves. The FEV_1 was measured from the same breath as that used for the MEFV either using a timing device displayed on the curve or a separate recorder. Statistical analysis of the results was carried out by M. J. Campbell and P. Oldham of the Pneumoconiosis Research Unit, Medical Research Council, Cardiff. Because only postinoculation function data were available in Sheffield, the details of 16 patients from this centre could not be included in this analysis. Of the remaining 70 patients failure to record function on one or more occasion reduced the number with complete records to 55, whose results were subjected to statistical comparison.

Serological methods. Blood was collected before and three weeks after virus inoculation for haemagglutinin-inhibition (HAI) tests against influenza A/Victoria/75 (H3N2) virus; all HI tests were carried out by Professor R. B. Heath at St Bartholomew's Hospital. The criterion of virus infection used was a greater than four-fold increase in the titres of HAI antibody following inoculation.

RESULTS

Evidence of infection

Table I shows the serological results for 86 patients who received either RIT 4050 virus or placebo; of these, 54 received virus and 32 placebo. Ten patients inoculated with virus developed infection, as shown by four-fold or greater increase in HAI antibodies, and these are listed in relation to the preinoculation HAI antibody titres in the table.

Table I. Serological response of volunteers to inoculation with influenza virus RIT4050 or placebo

Participating centres	*No. of patients*	*Inoculation*		*Serum HI responses of volunteers given RIT4050 virus*					
				>4-fold or more*			None or 2-fold*		
		Placebo	RIT4050 Virus	>16	16	>32	<16	16	>32
St Bartholomew's Hospital, London	14	5	9	1	2	0	3	1	2
Brompton Hospital, London	10	4	6	0	0	0	1	1	4
Hammersmith Hospital, London	16	6	10	0	0	1	1	3	5
Group Practice, Kingston-upon-Thames	26	10	16	3	2	0	9	1	1
Midhurst Medical Research Institute, Hampshire	4	2	2	0	1	0	0	1	0
Hallamshire Hospital, Sheffield	16	5	11	0	0	0	1	7	3
Total	86	32	54	4	5	1	15	14	15

* Preinoculation titres.

It was remarkable that of the 19 patients with preinoculation antibody titres less than 16 only 4 were infected by the vaccine virus; thus, the disappointingly low proportion of infections detected in these patients could not be attributed to high preinoculation antibody titres. The possibility existed that the necessary head-back position used for virus inoculation was not maintained adequately in these patients. The results of serological tests were used to divide the patients into three groups:

1. Those who received placebo and remained uninfected.
2. Those who received virus but failed to develop serological changes significant of infection.
3. Those who received virus and developed serological evidence of infection.

The 11 patients from the Sheffield centre who received virus were excluded from the analysis of clinical reactions because of the lack of pulmonary function tests in the preinoculation period. The results for the remaining 73 were analysed by preparing frequency tables for each symptom divided into numbers with no adverse response, adverse symptoms for more than 50% of the recording days and adverse symptoms on less than 50% of the days of observation. Calculation of expected numbers in each case, based on the proportion in each group compared with the proportions of the totals, showed no significant difference in the symptoms experienced by the three groups of patients (χ^2 test). The within-group variation in symptoms was high and there was no statistical evidence that those who were vaccinated and infected were symptomatically at a disadvantage following inoculation. In addition, no clinically adverse effects were encountered in any of the patients.

The results from 55 patients were accepted for analysis of pulmonary function. The data for each individual patient were graphed and found to exhibit fluctuations in all the various indices; these fluctuations occurred in all three groups of placebo, vaccinated without infection and vaccinated with infection. For each of the groups, the mean values of each lung function test were plotted against time. Two indices FEV_1 and V_{50} showed a drop in value in both placebo and vaccine groups. As the measurements on a single individual were correlated through time, the observation could not be regarded as an independent estimate of the value of the index in time. Linear contrasts were therefore calculated for each individual using a simple addition and subtraction of the individual measurements. Taking X as the value of a particular measurement of a particular day shown as a suffix, e.g., X_{21} for day 21, two linear contrasts (C1 and C2) of these measurements were calculated for each patient. Tables II and III show these contrasts as the mean levels for each index of pulmonary function, together with the standard error in each of the three groups of patients. Contrast C1 compares the mean levels of the various indices before and after vaccine, and C2 that of the first measurement after vaccine (X_7)

Table II. Mean values of $C1 = (X_{-21} + X_{-7})/2.0 - (X_7 + X_{21})/2.0$ (with standard errors)

Parameter	*Placebo*	*Vaccinated not infected*	*Vaccinated and infected*
No. analysed	19	28	8
FEV_1 (litres)	0.02 ± 0.047	0.060 ± 0.022*	−0.017 ± 0.036
FVC (litres)	0.041 ± 0.066	−0.001 ± 0.037	−0.066 ± 0.053
V_{50} (litres/sec)	0.086 ± 0.048	0.104 ± 0.050*	0.016 ± 0.058
V_{75} (litres/sec)	0.058 ± 0.033	0.014 ± 0.020	0.006 ± 0.024
PEFR (litres/sec)	0.053 ± 0.182	0.013 ± 0.086	−0.199 ± 0.147

A positive figure in these columns indicates a decline in function after inoculation.
* Denotes significantly different from zero.

compared with the mean level of the other four according to the formulae below. A positive figure in each column indicates a decline in function.

$$C1=(X_{-21}+X_{-7})/2.0-(X_7+X_{21})/2.0$$

$$C2=(X_{-21}+X_{-7}+X_0+X_{21})/4.0-X_7$$

Clearly on the null hypothesis that vaccine had no adverse effect, the expected value of either C1 or C2 would be zero. Fig. 1 shows C1 for each of the three groups of patients. For FEV_1 and V_{50}, the vaccinated but not infected groups had a significantly lower result after inoculation than before, but similar effect in V_{50} occurred in the placebo group. A small but non-significant rise in FEV_1 and FVC occurred in the vaccinated and infected group after inoculation. Thus, the analysis showed no significant deterioration in pulmonary function in those inoculated with RIT 4050 virus, whether or not they became infected.

Table III. Mean values$_{-7}$+X of $C2=(X_{-21}+X_0+X_{21})/4.0-X_7$ (with standard errors)

Parameter	*Placebo*	*Vaccinated not infected*	*Vaccinated and infected*
No. analysed	19	28	8
FEV_1 (litres)	0.032 ± 0.035	0.054 ± 0.017	−0.015 ± 0.032
FVC (litres)	0.057 ± 0.050	0.036 ± 0.039	−0.069 ± 0.050
V_{50} (litres/sec)	0.115 ± 0.055	0.066 ± 0.021	0.017 ± 0.047
V_{75} (litres/sec)	0.041 ± 0.022	0.023 ± 0.015	−0.004 ± 0.021
PEFR (litres/sec)	−0.161 ± 0.135	0.086 ± 0.108	−0.099 ± 0.093

A positive figure in these columns indicates a decline in function after inoculation.

* Denotes significantly different from zero ($P < 0.05$).

DISCUSSION

The results of the above and other trials of live attenuated influenza virus used as an intranasal vaccine in patients with chronic bronchopulmonary disease indicate both its relative safety and its effectiveness, but also show the limitations of this method of immunization. Effectiveness of live virus when used as a vaccine is usually estimated by its ability to raise the titre of serum HAI antibodies to a titre of 30–40 which is indicative of protection (Hobson et al. 1972), but changes which may also occur in nasal antibodies cannot so readily be correlated with susceptibility or resistance (Downie & Stuart-Harris 1970). In the present multicentre trial with RIT 4050 virus, and the earlier study using WRL 4050 virus (Fell et al. 1977), the single dose regimen failed to infect a high proportion of patients, whereas this virus did infect most normal young persons without or with low titres of homologous HI antibody. This could have been due to over-attenuation of the virus for infection of older persons with previous experience of the virus antigens. Alternatively, the failure could be a technical one due to the inability of patients with chronic bronchitis to hold the recumbent head-back position optimal for virus infection. The findings indicate that a multi-dose regimen should have been used.

The safety of live influenza virus vaccines for patients with chronic bronchitis must depend on the absence of clinically adverse effects; however, increased symptoms unaccompanied by alterations in pulmonary function could probably be tolerated, particularly in view of the known hazard of influenza in such patients. The delayed effects upon symptoms after inoculation with WRL 105 virus would probably have classified as 'tolerable' had not one patient exhibited an influenza-like illness (Fell et al. 1977). Thus, it is possible that the level of virus attenuation acceptable for healthy persons is at too high a threshold for those with disordered lower respiratory tracts; this could explain the findings for 4A2 virus which produced adverse effects on both symptoms and ventilatory function in patients with chronic bronchitis, in spite of the previous favourable tests in healthy volunteers (Winson et al. 1977). The high rate of infection obtained with this virus may also indicate that the virus could be less attenuated in virulence for patients with chronic bronchitis than for healthy persons.

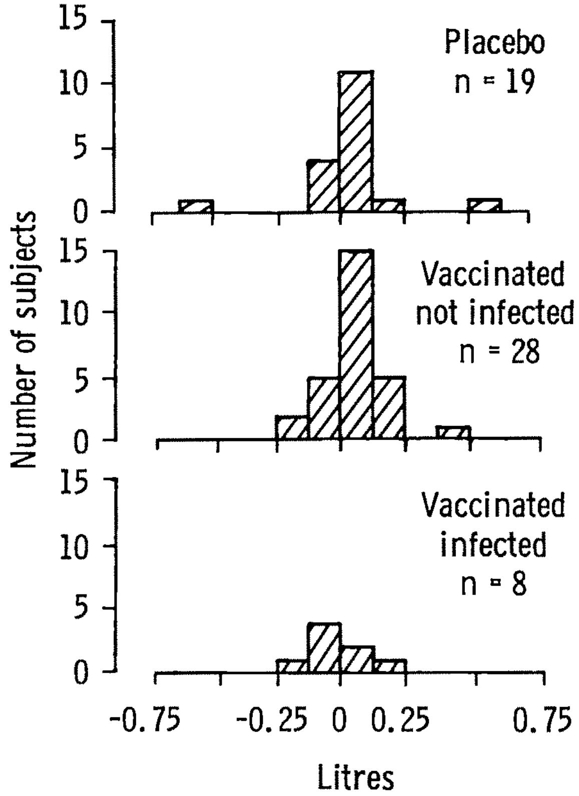

Fig. 1. Histogram of respiratory function test results. $C_1 = (X_{-21} + X_{-7}/2.0 - X_7 + X_{21})/2.0$. The histograms show only the results for the FEV_1; a positive value indicates a decline in FEV_1

The experience of our preliminary trials with live influenza virus vaccines was that there was sufficient variation in the measurements of indices of ventilatory function for it to be essential to study patients before and after virus inoculation using the same methods to give valid results. This phenomenon of variability of ventilatory function measurements in patients with chronic obstructive bronchitis may be a limitation of trials reported by other observers. Thus, Bartsch et al. (1977) studied RIT 4025 and RIT 4050 viruses in patients with chronic obstructive lung disease, asthma and emphysema, using spirometry to obtain flow volume curves, closing volume measurements for small airways function and the diffusing capacity; random fluctuations were noted in both studies, and the results were not considered with reference to virus infection and apart from the patients with asthma, the variations observed were thought to be within experimental error (Rosenzweig et al. 1975). The results of the ventilatory function tests in the present study showed a good order of consistency, and reproducibility was obtained in each centre. The method of statistical analysis of each index of function comparing the measurements obtained both before and after inoculation may be of value to others engaged in similar studies. The various tests proposed for measuring small airways function was not used in the present multicentre study because of the lack of reproducibility inherent in such tests, and the consequent difficulty in relating the results obtained in different studies.

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SULPHUR DIOXIDE IN FOODS AND BEVERAGES: ITS USE AS A PRESERVATIVE AND ITS EFFECT ON ASTHMA

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Summary

Sulphur dioxide is widely used in the food and drinks industries for its properties as a preservative and antioxidant. Whilst harmless to healthy persons when used in recommended concentrations, it can induce asthma when inhaled or ingested by sensitive subjects, even in high dilution. About one in nine asthmatics gives a history of asthma worsened by drinking 'soft drinks' containing sulphur dioxide. They are comparatively young and their asthma is predominantly extrinsic. The amount of sulphur dioxide in foods is limited by regulation in the UK, by directive in the EEC, and by recommendations to 'good manufacturing practice' in the USA. A list is given of foods and beverages commonly containing sulphur dioxide. These are predominantly dried fruits and vegetables, soft drinks and alcoholic beverages. Maximal permitted concentrations are quoted. Exposure to sulphur dioxide may also occur during the manufacture and preparation of foods and drinks in the factory, restaurant and home.

INTRODUCTION

Sulphur dioxide is widely used in the food and drinks industries. It has antibacterial and antifungal properties. It is a powerful reducing agent (antioxidant) and is used to inhibit oxidative processes associated with food spoilage. When used in gaseous form, it readily evaporates from solution leaving no residue. If used in foods and beverages in recommended concentrations and those laid down by statute it is normally harmless when ingested. However, some asthmatic subjects are sensitive to high dilutions of sulphur dioxide (SO_2) which do not affect normal subjects.

PROVOCATION OF ASTHMA

Experimental and environmental exposure to SO_2

Lawther (1955) described an experiment on a volunteer who was aware of his susceptibility to sulphur dioxide and who developed severe bronchospasm on inhalation of 2 ppm. Inhalation of sulphur dioxide in dilutions of 1–10 ppm causes bronchoconstriction in cats and dogs (Nadel et al. 1965; Islam et al. 1972). Inhalation of sulphur dioxide by healthy men caused in increase in airways resistance (AWR) at dilutions of 4 ppm upwards, and in one subject at 1 ppm (Frank et al 1962, 1964; Nadel et al. 1965; Abe 1967). The response in all instances was rapid, being observed at the first postinhalation measurement, within 4 minutes and in one instance at 10 seconds. Periods of increased atmospheric pollution with an increase in sulphur dioxide have been associated with an increased incidence of asthma attacks in adults (Zeidberg et al. 1961) and in children (Girsch et al. 1967). It is noteworthy that one of eleven supposedly healthy subjects reported by Frank et al. (1964), a 23-year-old male who gave a history of occasional wheezing with chest colds, and who developed an increase in AWR at a dilution as high as 1 ppm, also had by far the highest pretreatment AWR, and it seems likely that he was an asthmatic subject. A similar response occurred in one member of a group of supposedly healthy subjects reported by Nadel et al. (1965). His pre-exposure AWR was raised, which suggests that he too was asthmatic, and he became very wheezy after inhaling 5 ppm.

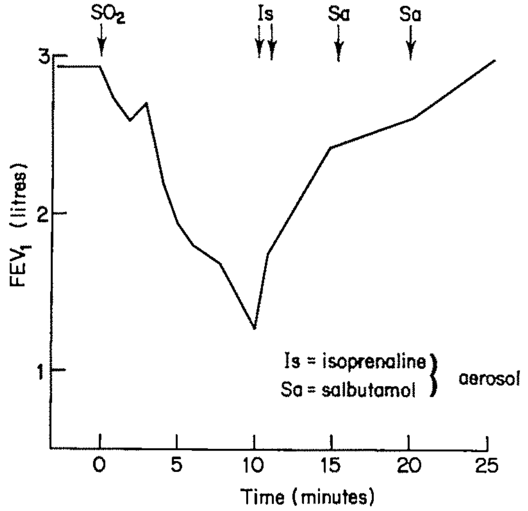

Fig. 1. Rapid onset of bronchospasm in a 16-year-old man following ingestion of 25 mg of SO_2 in 250 ml of water.

Ingestion of SO_2 in beverages

There is a single investigative report of the provocation of asthma by ingestion of SO_2 in beverages (Freedman 1977*a*). In this study of 272 asthmatic patients, 30 (11%) gave a history of exacerbation of the asthma induced by ingestion of orange drinks*. Fourteen of these 30 patients were challenged by drinking an aqueous solution of SO_2 in a concentration comparable to that permitted in orange drinks. Fig. 1 shows the response of one of these patients. There was an immediate fall in FEV_1 and 10 minutes after ingestion the FEV_1 was less than half the preingestion level. Of the 14 patients challenged, eight reacted with falls in FEV_1. A rapid onset of bronchospasm was the characteristic response of the eight SO_2-sensitive patients. Their mean age was 29 years, and in seven of the eight the asthma was intrinsic (Table I). Prior inhalation of sodium cromoglycate conferred protection.

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* In the UK the terms 'orange squash', 'orange crush' and 'orange drink' relate to the minimum orange juice content as laid down by The Soft Drinks Regulations (1964). In this article the term 'orange drink' comprises all categories.

SULPHUR DIOXIDE IN PRESERVATION OF FOODS AND BEVERAGES

SO_2 may be added as a gas, or it may be prepared in situ by adding sodium metabisulphite to acidic foods and beverages:

$$Na_2S_2O_5 + 2HR = 2NaR + H_2O + 2SO_2$$

In the UK, the Preservatives in Food Regulations 1975 (Statutory Instrument 1975 No 1487) list 47 categories of food which may contain SO_2. As some categories comprise several items many hundreds of different foods are probably included. The Regulations also state the maximum permitted concentrations of SO_2 for each category. The European Economic Community requires member states to conform to EEC Directive 64/54/EEC (5 November 1963) as regards preservatives for use in food intended for human consumption, and the above-mentioned UK Regulations implement the EEC Directive. In the United States the Food and Drug Administration's regulation 182.3862 does not set specific limits to the amount of SO_2 in foods, the use of which is permitted 'in accordance with good manufacturing practice'. Guidance on this is given in *Chemicals used in Food Processing* (1965) and by Chichester and Tanner (1975).

Table I. Responses of eight asthmatic patients to drinking a solution of SO_2 in water

Case	*Age*	*Sex*	*Type of asthma*	*Greatest fall in FEV$_1$* (%)	*Time of maximum fall* (min)†
1	64	F	Extrinsic	52	2
2	16	M	Extrinsic	57	10
3	52	F	Intrinsic	23	3
4	13	F	Extrinsic	37	5
5*	28	F	Extrinsic	35	25
6*	21	M	Extrinsic	12	25
7*	14	F	Extrinsic	12	5
8*	27	M	Extrinsic	17	10
mean	29			31	11

* In these patients protection against a fall in FEV_1 was conferred by prior inhalation of sodium comoglycate.

† Time elapsing between ingestion of SO_2 and greatest fall in FEV_1.

A selected list of the main categories of foods follows, together with their respective maximal permitted concentrations of SO_2. Unless otherwise stated these refer to UK Regulations, which may be consulted for the complete list. The convention is followed of expressing concentrations in parts per million (ppm), which is equivalent to milligrams per kilogram or per litre.

Vegetables. Peeled raw potatoes for making fried chips ('French fries'), 50 ppm. In the UK this is the only raw vegetable in which SO_2 may be used. In other countries raw carrots may be so preserved and also various canned vegetables (cabbage, peas, beans) where the SO_2 is used to preserve the natural colour. If these vegetables are cooked before the meal, they present no hazard to the SO_2-sensitive consumer, as the

SO_2 is expelled in the cooking. By the same token, the person who cooks the vegetable could be exposed to the SO_2 which is evolved. If the vegetables are eaten cold straight from the can, some evolution of SO_2 could occur while the food is eaten and could cause symptoms.

For dehydrated vegetables the UK limit is 2000–2500 ppm depending on type. For potato it is 550 ppm. In the USA the recommended limit is 250–2000 ppm depending on type. The US Army allows up to 4500 ppm (Schroeter 1966).

Fruit. In addition to its preservative action, SO_2 inhibits oxidative browning, a familiar example of which is the rapid colour change on the cut surface of a raw apple. Oxidative browning may be enzymatic, whereby colourless phenolic compounds are converted to coloured quinones, or it may be non-enzymatic whereby sugars are caramelized to coloured polymerizable furfural through a series of dehydration stages.

Of fresh fruits only grapes (15 ppm) may contain SO_2 in the UK. Elsewhere, sliced apple, peaches, pineapple, bananas, mango and papaya are treated, as are canned purées for baby foods. Symptoms have occurred following ingestion of fresh grapes, said to be intended for wine making and containing SO_2 above the permitted limit.

A 56-year-old housewife, who suffered from hay-fever, bought grapes from a street-trader. Immediately on eating the grapes, she was seized by a severe bout of coughing which lasted for several hours. This occurred outside the hay-fever season. Her non-atopic husband ate the grapes with impunity. The grapes were found to contain an excess of SO_2.

In 1974 four patients with asthma suffered an exacerbation of symptoms after eating grapes purchased in a street market. Analysis again showed an excess of SO_2.

Dried lilies, imported from China and used as a vegetable in Chinese restaurants, have been found to contain excess SO_2.

For dried fruit the UK and USA limits are 2000 ppm or less depending on the type of fruit, except in the US Army where it is 4500 ppm (Schroeter 1966). Whilst 2000 ppm may be the initial SO_2 concentration in, for example, raisins, the SO_2 concentration will be much reduced by the time they have been washed, hot-air dried and packed, and 100 ppm would be exceptional. This, however, is not necessarily the case with dried fruit intended for cooking.

A 32-year-old housewife who suffered from extrinsic asthma and was sensitive to orange squash, ate some dried apricots intended for soaking and stewing. This was promptly followed by an attack of asthma.

Fruit juice. Whether concentrated or not, the limit is 300 ppm, except for (*a*) concentrated grape juice for home wine-making, 2000 ppm, and (*b*) grape juice for sacramental use, 70 ppm.

Sugars and syrups. 20–400 ppm, according to type, the higher concentration for use in the manufacture of confectionary. The limit for jam, is 100 ppm.

Meats and fish. The use of SO_2 in meats is prohibited in the USA. Sausages and sausage meat are the only meat products in which it may be used in the UK and here the limit is 450 ppm. In Canada sulphites are allowed in poultry and certain meat products. Sulphites may be used in shrimp in the USA and in France and in dried fish in France. The objection to the general use of SO_2 in meat is that it can restore a faded colour to that of fresh meat (Chichester & Tanner 1975). In fact, sodium nitrate or nitrite are preferred for the preservation of meats.

Dairy products. Fruit yoghurt (60 ppm) is the only permitted dairy product in the UK. Elsewhere, milk powder is treated.

Soft drinks. These constitute a large and important category. The SO_2 limit is 70 ppm in those that are ready to drink and 350 ppm in those intended for dilution. All citrus soft drinks, as well as others in which there is no fruit juice, such as lemonade and the other '—ades', may contain SO_2. 'Ribena' (150 ppm), a concentrated blackcurrant syrup, and 'Lucozade' (50 ppm), an orangeade type drink, both very popular in the home and on the hospital bedside locker, also contain SO_2, as do many similar proprietary drinks.

In commercial practice a high concentration of SO_2 is needed for the preservation of damaged fruits. Before the juice can be used for various purposes, the concentration of SO_2 can be reduced ('desulphitization') by passing carbon dioxide through the juice (Schroeter 1966). Hence, it seems possible that 'carbonated' (fizzy) drinks and sparkling wines, which contain carbon dioxide in solution under pressure, may yield their SO_2 more rapidly than still drinks when the pressure is lowered prior to consumption.

Alcoholic beverages. Sulphur dioxide plays an essential role in the manufacture of alcoholic beverages. It is used to sterilize equipment, to restrain unwanted micro-organisms and to disperse cloudiness. When the beverage is matured and ready for drinking, SO_2 helps to maintain flavour and colour and to discourage the growth of contaminating organisms. In the UK the permitted upper limit of SO_2 in beer is 70 ppm, and in cider and perry it is 200 ppm. In wine the upper limit is 450 ppm. Here we must surely have a potent source of irritant to account for some cases of asthma due to wine-drinking.

EXPOSURE TO SO_2 DURING MANUFACTURE AND PREPARATION OF FOODS AND BEVERAGES

Persons who are sensitive to SO_2 are at risk of experiencing symptoms if they are involved in the manufacture or preparation of foods and beverages containing the gas or one of its precursors.

Raw vegetables

A 44-year-old man suffering from intrinsic asthma was proprietor of a shop selling fried fish and chipped potatoes. If he used potatoes supplied to him raw and 'sterilized', the asthma worsened immediately after plunging the potatoes into hot oil.

Soft drinks

A middle-aged man suffering from mild but long-standing asthma was employed at the factory of a leading British manufacturer of soft drinks. Whenever he entered the area where SO_2 was used, he experienced a prompt worsening of the asthma.

Dehydrated vegetables

A 23-year-old male hop-sampler had suffered from asthma since the age of 12. Sampling dried, preserved hops induced mild asthma and fairly severe rhinitis. Dehydrated hops may contain SO_2 up to 2000 ppm. Symptoms ceased after changing his occupation.

Wine. The manufacture of wine deserves special mention. Metabisulphite is used during wine-making and there is a possibility of exposure to SO_2, especially by amateurs at home. Metabisulphite is available both as 'Campden tablets', which contain approximately 0.5 g of the substance, and in powder form, from which a 10% stock solution is prepared for further dilution before use. It is used at an SO_2 equivalent of 50 ppm during the primary fermentation of the must to suppress wild yeasts and micro-organisms which produce unwanted acetic and lactic acids while allowing the wine-yeast to multiply. Double this concentration of SO_2 is used for pulped fruit, and treble for bruised fruit. Metabisulphite is also added during serial decantations (racking) of the must. SO_2 is partially bound to glucose and acetaldehyde and this may entail supplements of metabisulphite to maintain the level of free SO_2. SO_2 promotes the formation of glycerol which endows the product with 'body' and 'smoothness' (Duncan & Acton 1967). It also aids clarification of the wine by precipitating colloid and inhibits oxidative browning which is especially prone to affect over-ripe fruit.

Beer brewing and wine making at home have become popular hobbies in recent years and an appreciable risk to asthmatics from exposure to SO_2 may lie in these domestic activities. In addition to its use in the control of fermentation, metabisulphite is used in 10% solution to sterilize equipment. It is swirled around the interior of containers and applied to the exterior surfaces of equipment by wiping with a cloth dipped in the solution. It has an irritant and pungent odour which can be quite disagreeable when used in a small or poorly ventilated room even to those without asthma. Some home wine makers add citric acid to the metabisulphite before use in sterilizing, which causes a more rapid evolution of SO_2 into the ambient air.

Discussion

Many foods and beverages contain SO_2 and one is led to speculate on the causal relationship between this preservative and apparantly cryptogenic asthma or asthma wrongly ascribed to specific food allergies. In patients with an inconsistent or paradoxical history of asthma occurring after a specific food which at other times is eaten with impunity, the presence of a food additive should be suspected as the responsible agent. The simplest approach to this clinical problem is to put the patient on a trial diet free from preservatives (Freedman 1977*b*). A cardinal feature of SO_2-induced asthma is rapidity of onset of symptoms, usually within a few seconds to two minutes. Whilst this time-course may occur with food allergies, an interval of more than 30 minutes between ingestion and onset of symptoms would exclude SO_2 as the cause.

Soft drinks which may cause asthma, may contain additives other than SO_2 capable of provoking asthma, notably the preservative sodium benzoate and various dyes of which tartrazine, sunset yellow, amaranth and ponceau 4R (new coccine) are in frequent use (Freedman 1977*a*). However, the interval between ingestion of these substances and the onset of asthma is usually greater than half an hour. When asthma follows wine drinking one must consider as possible causes, in addition to SO_2 and alcohol, specific allergy to yeast products and to the various substances used as finings (to clarify by precipitation of suspended colloid), for example isinglass (fish), casein (milk), albumen (egg), ox blood (beef) and gelatin (various animal sources). The manufacture of sauterne wines involves colonization of the must by the mould *Botrytis cinerea* to which a patient may harbour specific antibodies.

In the industrial environment the maximal permitted concentration of SO_2 in the ambient air is 5 ppm. However, in 1978 a notice was published of intended changes limiting the short-term exposure to 5 ppm and long-term exposure to 2 ppm. These concentrations of SO_2 are capable of provoking asthma in sensitive persons. It is in the restaurant or in the home where food is prepared or wine is made under uncontrolled environmental conditions that asthma seems more likely to be provoked.

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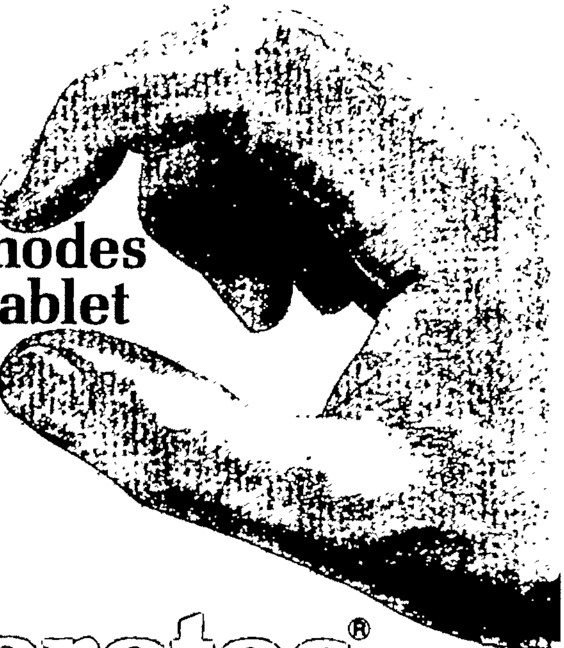

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CONTROLLED TRIAL OF THE EFFECT OF REPEATED ADMINISTRATION OF IPRATROPIUM BROMIDE ON VENTILATORY FUNCTION OF PATIENTS WITH SEVERE CHRONIC AIRWAYS OBSTRUCTION

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Summary

A trial was designed to assess whether repeated administration of ipratropium bromide for two weeks produced greater improvement than was obtained after a single dose. The effect of ipratropium bromide was compared with that of a placebo during a double-blind cross-over randomized trial in patients with advanced chronic airways disease in a stable state. Ipratropium bromide and placebo were both administered by metered dose inhaler for 14 days. There was a slight statistically significant improvement of conductance, thoracic gas volume, FEV_1 and VC after inhalation of ipratropium bromide, but repeated doses of the drug did not produce progressive improvement.

Introduction

Some anticholinergic agents are very active bronchodilators with respiratory effects comparable to those of beta-sympathomimetics (Altounyan 1964; Quanjir & Tammeling 1972). Their use by a systemic route is, however, limited by their well known side-effects; these can be reduced when the drugs are given by aerosol. Ipratropium bromide, an atropine derivative (Engelhardt & Knapp 1975) given by metered dose inhaler, is highly active and is well tolerated (Ulmer 1971; Bauer & Kummer 1973; Minette et al, 1973; Poppins & Salorinne 1973; Schindl 1973).

The purpose of this trial was to compare the effect of this drug with placebo on different aspects of pulmonary function during a period of regular administration over two weeks.

Material and Methods

Ten male patients suffering from chronic airways obstruction in a stable state (i.e. outside exacerbations), were included in the trial.

Before starting the trial, the reversibility of the airway obstruction was tested by inhalation of atropine methylnitrate (AMN) and fenoterol in every case. The increase of the airway conductance reached at least 20% 15 minutes after administration of one of the two bronchodilators.

The trial consisted of a double-blind cross-over comparison of ipratropium bromide and placebo, each administered in random order for 13 days. The dose was two puffs five times a day from a metered dose inhaler at regular intervals between 09.30 and 22.30 hours.

Specific airway conductance (SGaw), volume of thoracic gas (VTG), forced expiratory volume in one second (FEV_1), slow vital capacity (VC), the slope of the alveolar plateau of the nitrogen washout curve after a VC inspiration of oxygen (ΔN_2) were measured at 09.00 and 11.30 hours (i.e. before the second dose), on Days 4 or 5, 8 or 9 and 12 or 13 of each period.

On the thirteenth day of each period pH, Pa_{O_2} and Pa_{CO_2} of arterial blood and total lung capacity (TLC) (by plethysmography and by the multiple breath helium dilution method) were measured.

In six patients the reversibility of airway obstruction after atropine methylnitrate was again measured on the thirteenth day of each period.

For FEV_1 and lung volumes, the predicted values of CECA (1971) have been used, for SGaw, those of Pelzer and Thomson (1966) and for ΔN_2, those of Buist and Ross (1973). The reference value for VTG was assumed to be 55% of the predicted TLC.

The evaluation of symptoms was based on a daily interrogation by a physiotherapist concerning degree of dyspnoea, frequency and severity of cough and frequency, appearance and quantity of sputum. For each symptoms a score was calculated (Weibren et al. 1969).

The patients were asked about possible side effects such as dry mouth and disturbances of vision, heart beat or micturition.

Sympathomimetics and anticholinergic agents other than ipratropium were discontinued during the study but administration of antibiotics (two patients), digitalis (two patients), diuretics (one patient) and theophylline suppositories (six patients) was continued as well as physiotherapy and aerosol administrations of isotonic saline solution (eight patients). Two patients were treated with corticosteroids, the dosages of which were adjusted according to symptoms.

The results were evaluated by analysis of variance with orthogonal decomposition of the effects and by regression analysis of the different results on the different days of testing.

RESULTS

The characteristics of the 10 patients and the results of initial lung function tests before the trial are shown in Table I. Table II shows the effects of fenoterol (400 μg) and of atropine methylnitrate (2 ml of 3.2% solution by aerosol) before starting the trial. The effects of these two bronchodilators on the SGaw and on the VTG were small but statistically highly significant.

Table III shows the results obtained with placebo and ipratropium on the different test-days and Fig. 1 illustrates the comparison of the means calculated for each treatment period at 09.00 and 11.30 hours.

From the different sets of data, comparisons were made and regressions calculated, according to orthogonal decomposition of the effects using analysis of variance.

At 11.30 hours, SGaw, FEV_1 and VC were significantly higher and VTG was significantly lower during ipratropium treatment than during placebo treatment. On the other hand there was no significant difference of ΔN_2 values between both treatments.

At 09.00 hours, SGaw, FEV_1, VTG and VC did not differ significantly from one period to the other. On the contrary, ΔN_2 was significantly higher during ipratropium treatment than during placebo treatment.

Table I. Lung function (mean values) of 10 patients before the trial

Age (years)	58.9	TLC He (% predicted)	115.9
Height (cm)	167.4	SGaw (% predicted)	5.45
Weight (kg)	60.2	VTG (% predicted)	207.7
VC (% predicted)	62.5	ΔN_2 (% predicted)	839.9
FEV_1 (% predicted)	25.2	Pa_{O_2} (mmHg)	64.9
FEV_1/VC (%)	27.3	Pa_{CO_2} (mmHg)	45.9
RV (% predicted)	246.1	pH	7.38

Table II. Acute effects of inhalation of fenoterol and atropine methylnitrate on mean values of specific airway conductance (SGaw) and volume of thoracic gas (VTG)

	Fenoterol (400 μg)			*Atropine Methylnitrate* (2 ml of 3.2% solution)		
	Before	After 15 min	*P*	Before	After 15 min	*P*
SGaw						
kPa/sec × 10^2	18.1	25.9	0.001	15.4	26.7	0.001
% predicted	6.7	9.6		5.7	9.9	
VTG						
ml	6500	6130	0.004	6440	6040	0.010
% predicted	193 9	178.3		190.8	179.2	

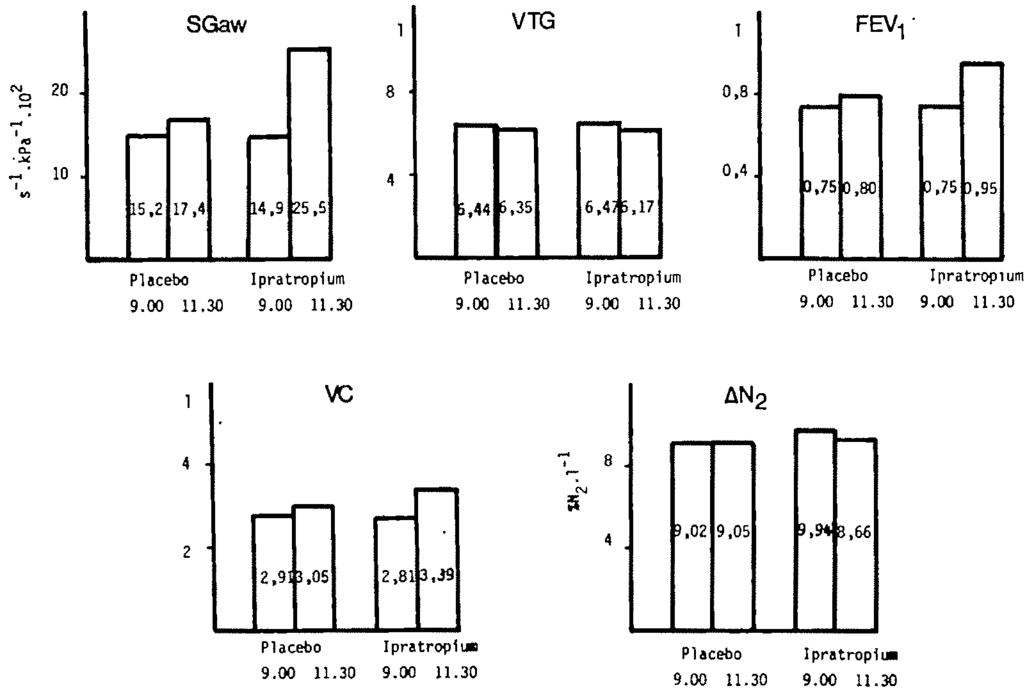

Fig. 1. Mean values of lung function tests at 09.00 and 11.30 hours during administration of ipratropium and placebo

During placebo treatment, SGaw and FEV_1 were significantly higher at 11.30 than at 09.00 hours but, for VTG, VC and ΔN_2 no significant difference was observed between 09.00 and 11.30 hours. None of the regressions of the different variables measured at 09.00 and 11.30 hours on the different test days was statistically significant.

There were no significant differences in total lung capacity or arterial blood $P\text{co}_2$ or $P\text{o}_2$ measured at the end of each treatment period. The difference of about 5% between

Table III. Measurements (mean ± SD) on different days of the trial

Time of measuring	*Variables and units*	*Ipratropium bromide*				*Placebo*			
		Day 4	Day 8	Day 12	Regression P	Day 4	Day 8	Day 12	Regression P
09.00	SGaw (kPa/sec × 10^2)	13.5 ± 3.7	16.2 ± 3.4	15.0 ± 5.7	0.40	15.7 ± 5.6	15.2 ± 4.3	14.7 ± 5.4	0.44
	VTG (ml)	6660 ± 860	6320 ± 770	6420 ± 890	0.07	6440 ± 630	6470 ± 660	6420 ± 830	0.78
	FEV_1 (ml)	710 ± 230	790 ± 290	760 ± 310	0.41	770 ± 220	740 ± 230	740 ± 240	0.58
	VC (ml)	2740 ± 440	2870 ± 680	2820 ± 610	0.72	2830 ± 540	2940 ± 450	2970 ± 520	0.27
	ΔN_2 (%N_2 litre)	10.4 ± 2.8	9.5 ± 3.4	9.9 ± 3.8	0.16	9.0 ± 2.9	9.3 ± 3.1	8.7 ± 2.6	0.74
11.30	SGaw (kPa/sec × 10^2)	23.2 ± 12.1	27.1 ± 9.8	26.2 ± 11.6	0.08	19.5 ± 9.2	16.7 ± 4.1	16.1 ± 5.6	0.09
	VTG (ml)	6190 ± 730	6140 ± 770	6180 ± 720	0.98	6290 ± 810	6310 ± 780	6460 ± 770	0.18
	FEV_1 (ml)	920 ± 340	990 ± 380	940 ± 310	0.63	830 ± 300	800 ± 230	780 ± 230	0.46
	VC (ml)	3300 ± 550	3480 ± 590	3410 ± 570	0.75	3070 ± 550	3090 ± 540	2990 ± 440	0.59
	ΔN_2 (%N_2 litre)	9.4 ± 3.0	8.2 ± 2.6	8.4 ± 2.4	0.09	9.0 ± 2.2	9.1 ± 2.5	9.0 ± 2.2	0.99

the results of measurement of TLC by the two methods was statistically significant but did not differ between ipratropium and placebo periods.

Atropine methylnitrate was administered to six patients at the end of each treatment period immediately after the 11.30 hours measurements, that is two hours after ipratropium bromide or placebo administration, and SGaw and thoracic gas volume were measured again 15 minutes later.

This additional dose of atropine methylnitrate produced a statistically significant further increase of SGaw and fall of thoracic gas volume at the end of both ipratropium therapy and placebo aerosols. SGaw increased from 21.7 to 36 kPa/sec/10^2 (from 8.2 to 13.5% of predicted) at the end of the ipratropium period and from 14.2 to 29 kPa/sec/10^2 (5.3 to 10.9% of predicted) at the end of the placebo period.

Daily symptom scores for breathlessness, cough and sputum volume and appearance did not differ between the ipratropium and placebo periods.

Intake of other drugs during the trial

Steroids: Two patients were treated with prednisolone. The first ingested a total of 60 mg during the placebo period and a total of 144 mg during treatment with ipratropium bromide. The second patient received 112 mg during the placebo period and 16 mg during ipratropium treatment. In both cases, the higher dosages were administered during the first two weeks of the trial.

Theophylline: Six patients regularly received theophylline (350 mg in suppositories). There was no difference between the administered dosages during the placebo and treatment periods.

Antibiotics: Three patients received antibiotics during treatment with ipratropium.

Side effects

During ipratropium bromide treatment, four patients mentioned dry mouth and one had symptoms attributed to abnormalities of ocular accommodation during both periods of the trial. No patient had mydriasis or difficulties with micturition. Two patients reported difficulty with expectoration, one during both periods of the trial, the other only with placebo.

DISCUSSION

All patients examined in this trial had severe chronic airways obstruction with hyperinflation of the lungs and major disturbances of gas distribution. A small but statistically significant reversible component could be demonstrated in all patients by means of SGaw increase following a single dose of fenoterol and atropine methylnitrate administered by aerosol. The purpose of the trial was to assess whether repeated administration of ipratropium bromide for 13 days produced a greater improvement than that obtained after a single dose.

To evaluate persistence of the effect of ipratropium bromide measurements at 09.00 hours during each period were compared. The SGaw, VTG, FEV_1 and VC values did not differ significantly between the treatments. There was a slight worsening of ΔN_2 with ipratropium bromide, possibly due to a late rebound effect occurring many hours after the last administration of the drug. The lack of regression with time of all the measurements performed at 09.00 shows that there is neither a progressive improvement nor a progressive deterioration from the basic state during treatment.

The acute effect of ipratropium bromide may be assessed by comparing measurements performed at 11.30 hours (two and a half hours after the administration of the drug) with those at 09.00 hours. This comparison, however, includes any possible placebo effect and spontaneous diurnal variations. In order to eliminate these factors, the results obtained at 11.30 hours during ipratropium bromide treatment were compared with those at 11.30 hours during the placebo period. The comparisons of the SGaw, VTG, FEV_1 and VC values showed a significant reduction ot airway obstruction and of pulmonary distension under the effect of ipratropium bromide. As to ΔN_2, an improvement with ipratropium bromide was seen by comparing measurements at 11.30 and at 09.00 hours but not between serial measurements at 11.30 hours. This could simply be the result of the absence of the possible rebound effect seen at 09.00 hours during treatment with ipratropium.

The lack of regression with time of the values at 11.30 hours discounts any acquired tolerance and also any progressive improvement with ipratropium.

During the administration of placebo none of time regressions is significant and the patients' condition seems therefore not to have changed during this period. However, a significant improvement of FEV_1 and SGaw occurred between 09.00 and 11.30 hours: this could be attributed either to a placebo effect, or to diurnal variation or to both. These effects which are similar to those observed by Zedda and Sartorelli (1971) represent only 25% of that observed after ipratropium bromide.

The differences observed between TLC as measured by plethysmography and by helium dilution (corresponding to trapped air) were similar during administration of ipratropium and placebo. There was also no difference in arterial gases during the two periods. This suggests that the administration of a bronchodilator does not fundamentally modify pulmonary function of patients with advanced obstructive airway disease. This is not surprising since the therapeutic action of ipratropium bromide is limited to an acute effect on the bronchospastic component, which represents only a small fraction of the overall abnormalities of function of patients whose ventilatory deficit is mainly irreversible.

The effects of atropine methylnitrate and of fenoterol on the thoracic gas volume and the effects of ipratropium bromide on vital capacity and thoracic gas volume are in favour of an at least partially peripheral site of action of these drugs. This result has been observed by most of the authors who studied ipratropium bromide with the exception of Yernault et al (1975).

In six patients who received atropine methylnitrate two and a half hours after the administration of ipratropium bromide, an additional increase of the SGaw was observed. Several hypothesis may explain this phenomenon: either the administered dose of ipratropium bromide was insufficient to produce a maximal effect, or the bronchodilating effect of ipratropium bromide had partially subsided after two and a half hours, or the bronchodilating effect of ipratropium improves the penetration of the subsequent atropine methylnitrate aerosol. According to this third hypothesis, it could be therapeutically useful to administer a second dose of a bronchodilator when the maximum effect of the first dose is reached.

Analysis of variance indicates the respective sensitivity of the different measurements used. The SGaw appears to be most sensitive, followed in a decreasing order by the FEV_1, the VC and the thoracic gas volume. Compared to these values, the ΔN_2 is relatively insensitive for the bronchodilating effect of ipratropium bromide and is likely to reflect the existence of irreversible abnormalities.

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CORTICOSTEROIDS IN CHRONIC AIRWAYS OBSTRUCTION: CAN THE PATIENT'S ASSESSMENT BE IGNORED?

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Summary

In a study to examine the methods of assessing the response of patients with chronic airways obstruction to corticosteroids, 20 patients received a week of placebo tablets, followed by three weeks of prednisolone 30 mg daily. Subjective benefit was assessed by a visual analogue scale (VAS), and objective changes by spirometry and an exercise test. Significant increases in FEV_1 and in exercise performance were observed after steroid therapy. Changes in FVC correlated both with VAS score and with changes in exercise performance. Changes in FEV_1 correlated with neither. The good correlation between the changes in a ventilatory function test (the FVC) and the patients' assessments of the drug suggests that the non-specific euphoriant effect of steroids does not eclipse their specific action on ventilatory function. Assessment of benefit should include a subjective assessment and changes in FVC and exercise performance. Changes in FEV_1 appear to have less clinical relevance.

INTRODUCTION

Patients with chronic airways obstruction often receive a trial of corticosteroids, i.e. a short course of steroids in high dose. This identifies the occasional patient who shows an impressive improvement and who therefore qualifies for the diagnosis of asthma. At the other end of the spectrum of airways obstruction is the patient who receives no benefit from the drug. Between these two polar groups are patients who display slight spirometric benefit and, more difficult, those who display little spirometric improvement but claim considerable subjective benefit. The clinician then has to decide what constitutes a response to treatment and whether to continue with a potentially dangerous drug.

This study was not intended to assess whether steroids do or do not improve airflow in chronic airways obstruction; the aim was to examine the methods of assessing responses to treatment.

Patients and Methods

Twenty patients (19 male) with chronic bronchitis according to the criteria of the Medical Research Council (1965) were studied. All had chronic airways obstruction, the mean FEV_1/FVC ratio being 36% (range 24–51). The mean FEV_1 ± SD (and range) was 980 ± 290 (500–1500) ml, and the mean FVC was 2720 ± 500 (1950–3600) ml. After inhalation of 200 μg of salbutamol, the increase in mean FEV_1 was 13 ± 12 (−5–37)%. In three patients the increase exceeded 20%, but in no case did the post-bronchodilator FEV_1 reach 60% of the predicted value.

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FEV_1 and FVC were measured on a Vitalograph spirometer (Drew & Hughes 1969), the best of three readings being taken and expressed at body temperature and pressure, saturated. Exercise tolerance was measured by a self-paced walking test, in which the patient was required to cover as much ground as he could, walking along a level corridor for 12 minutes. This test had been described as a simple and reproducible index of respiratory disability provided that a practice attempt is allowed (McGavin et al. 1978).

The subjective benefit from the steroid trial was assessed by a visual analogue scale (VAS). At the end of each treatment period, the patient was shown a 100 mm line labelled 'very very much worse' at one end, 'very very much better' at the other end, and 'before treatment' at 50 mm. He was asked to indicate the point on the line corresponding to the change he had experienced. The results were expressed as the distance in mm of the point along the line.

The patients attended for tests on three occasions at approximately the same time of day. On each occasion FEV_1, FVC and 12 minute walking distance (12 MD) were measured. The patient then inhaled 200 μg of salbutamol aerosol and, after a 20 minute rest, measurements of FEV_1, FVC and 12 MD were repeated. After the first day's tests, the patients were given a seven day course of dummy tablets equivalent to prednisolone 30 mg daily. This was done in order to establish a steady base-line, to allow practice at the tests and to allow for the placebo effect of tablets. All the tests were repeated at the end of the dummy period and again after three weeks of prednisolone 30 mg daily.

Statistical analyses were Student's *t*-test for paired observations and calculation of linear correlation coefficients by the method of least squares. The analyses were carried out on the second observations on each day, i.e. after bronchodilatation.

Table I. FEV_1, FVC, 12 MD and VAS score before and after therapy (mean ± SD)

	FEV_1 (litres)	*FVC* (litres)	*12MD* (m)	*VAS*
Before therapy	1108 ± 331	3177 ± 709	869 ± 227	—
After placebo	1152 ± 364	3191 ± 706	886 ± 234	+9 ± 19
After prednisolone	1250 ± 477	3319 ± 823	957 ± 209	+19 ± 24

RESULTS

After the week of dummy tablets, no significant changes occurred in FEV_1, FVC or 12 MD (Table I). The tablets had a placebo effect as judged by the VAS assessment which showed a mean shift of 9 mm towards improvement (Table I). Such changes as occurred in spirometry and 12 MD do not correlate with the VAS score.

After three weeks of steroid therapy, significant increases were observed in FEV_1 and 12 MD (Table I): mean FEV_1 rose by 8% (98 ml, $P < 0.02$) and mean 12 MD rose by 8% (71 m, $P < 0.02$). The increase in mean FVC (128 ml, 4%) was not significant. Data from the subjective assessment by the VAS are shown in Fig. 1, the mean increase being 19 mm. There is a suggestion of a bimodal response with a division at approximately +25 mm.

Correlations between VAS score and objective assessments are shown in Table II. Changes in FVC are well correlated with VAS ($P < 0.001$) and less closely with changes in 12 MD ($P < 0.05$). VAS score is correlated with changes in 12 MD only at the 10% probability level. Changes in FEV_1 are correlated with neither VAS nor changes in 12 MD ($r = 0.05$).

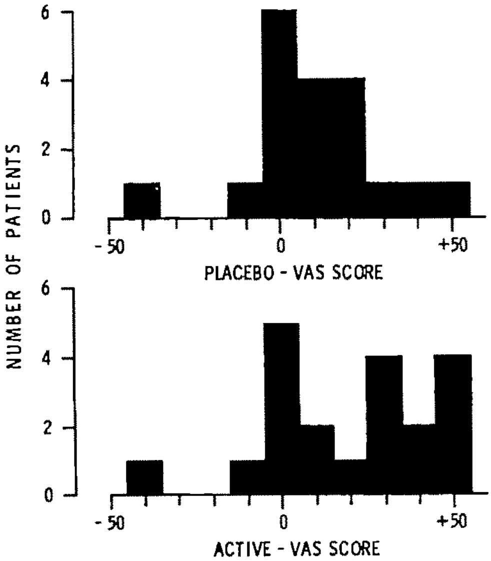

Fig. 1. VAS scores after placebo and after active steroid

Table II. Correlation coefficients (r) between % changes in FEV_1, FVC, 12 MD and VAS after steroid therapy

	12 MD	*FVC*	*FEV_1*
VAS	0.38	0.72*	0.35
12 MD		0.56†	0.05

* = $P < 0.001$.
† = $P < 0.05$.

Table III. Percentage change in FEV_1, FVC and 12 MD according to VAS score (mean ± SD)

VAS	*< +25 mm*	*> +25 mm*	*P*
n	10	10	
FEV_1	6±13	9±14	NS
FVC	−4±16	12±10	0.05
12 MD	3±7	18±20	0.025

Table III shows a comparison of changes in FEV_1, FVC and 12 MD between those patients who gave a VAS score of less than +25 mm improvement and those who gave a score of +25 mm or more. The significance of the differences has been assessed by comparing the means between the group using a *t*-test. The results emphasise the lack of relationship between changes in FEV_1 and symptoms. Figs 2 and 3 illustrate the changes in VAS score and in spirometry.

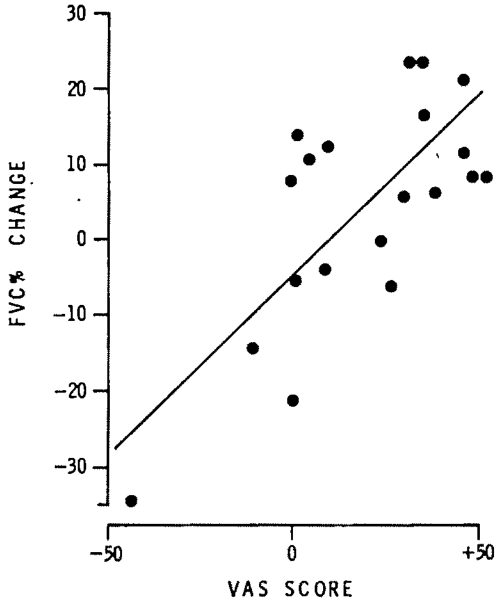

Fig. 2. Percentage change in FVC plotted against VAS score after steroids

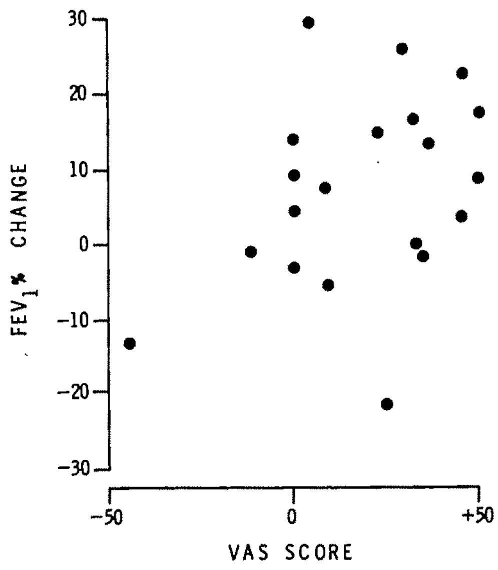

Fig. 3. Percentage change in FEV_1 plotted against VAS score after steroids

DISCUSSION

The aim of this study was to examine methods of assessing benefit from corticosteroids in patients with chronic airways obstruction. The initial week on dummy tablets was incorporated into the design in order to assess the placebo effect whilst establishing a steady base-line of objective assessment. The further three weeks of active drug treatment reflect the way in which steroid trials are commonly conducted in clinical practice. No attempt was made to compare the effects of dummy and active tablets.

The accurate assessment of the effect of steroids in patients with chronic airways obstruction is important in order to avoid long-term administration in cases where there is no benefit. Because of the euphoriant effect of steroids in some patients clinicians tend to regard a subjective assessment with suspicion and rely on ventilatory function tests. The assessment has to be more critical than with simple bronchodilators which do not have a euphoriant effect or long-term side-effects. Freedman (1963) studied changes in FEV_1 in 25 subjects with airways obstruction and stated that 'the euphoriant effect of the prednisolone led to a number of grossly inaccurate assessments in patients whose FEVs diminished or remained the same'. He did not question whether the FEV_1 was the best yardstick for judging improvement. Sahn (1978) has reviewed 17 studies of the effects of steroids in chronic bronchitis and emphysema and has divided the studies into six which showed a positive effect and 11 in which corticosteroids were unhelpful. In many of the 11 negative studies, the index of failure appears to have been a lack of increase in FEV_1 but in seven of these studies, a 'positive clinical response' was noted. There have been no attempts to quantify the subjective response so as to allow a statistical assessment. The question arises whether the FEV_1 is the best guide to the patient's response and whether the subjective assessment should be ignored.

We have used a visual analogue scale in an attempt to quantify the subjective assessment and to compare it with objective changes. The visual analogue scale has been described and used as a measure of emotional feelings by Aitken (1969), and has been found satisfactory in the assessment of other subjective sensations such as pain (Joyce et al. 1975). Using this technique, we have found that the results of a ventilatory function test, namely the FVC, were well correlated with subjective assessment and to a lesser extent with changes in exercise performance. This suggests that these three phenomena are inter-related and form a useful basis for assessing a response to steroids. The failure of the FEV_1 to fit in with this scheme requires consideration because this measurement is put forward as a reproducible and relatively effort-independent measure of airflow. One explanation is that the vital capacity, the subjective assessment and exercise performance are all subject to the euphoriant effect of steroids and that the FEV_1, being effort-independent, is the only valid assessment. However, it is open to question whether the FEV_1 is a good index of respiratory disability, as opposed to airflow obstruction. There is increasing evidence that in patients with chronic airways obstruction exercise performance is not well correlated with the FEV_1 but can be better judged from a subjective assessment and the vital capacity (Leitch et al, 1978; McGavin et al. 1976, 1978; Newton & Bevans 1978). In short-term studies in patients with airways obstruction exercise tolerance has been measured before and after the administration of drugs which do not have a euphoriant effect such as simple bronchodilators and β-adrenergic blocking drugs. In these studies changes in exercise performance correlated better with changes of vital capacity than of FEV_1 (McGavin & Williams 1978; McGavin 1980).

Mungall and Hainsworth (1979) have investigated the variability of lung function tests and exercise performance in 13 patients with chronic airways obstruction, making six observations at intervals of two to three weeks. They found that the most reproducible test was the 12 MD with a coefficient of variation of $\pm 4.2\%$. The variability of the FEV_1 ($\pm 15\%$) was greater than that of the vital capacity ($\pm 11\%$). It seems that the FEV_1 can vary quite widely in chronic airways obstruction without having a direct effect on exercise performance.

In a previous paper (McGavin & Williams 1978), we discussed the suggestion that the peak flow rate and FEV_1 reflect airflow in larger airways while changes in FVC reflect alterations in calibre or patency in the smaller airways in patients with airways obstruction (see also Green 1978). It may be that these patients are very sensitive to alterations in their vital capacity in that the factors affecting vital capacity are also important in the sensation of dyspnoea and in the determination of exercise tolerance. Tests which measure flow rates in the larger airways on forced expiration do not seem so relevant in the assessment of these factors. Thus, in Freedman's study (1963) it may have been the FEV_1 rather than the subjective impression which gave the 'inaccurate' assessment.

It is of greatest importance to the patient with chronic airways obstruction how breathless he feels and how fast he can walk. In this study both these observations correlated with changes in vital capacity after steroids. It would seem reasonable to use a combination of these assessments to judge the response of patients with chronic airways obstruction to steroids. By contrast, the FEV_1, a reproducible measure of the performance of larger airways on forced expiration, would seem to have less clinical relevance.

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ASTHMA AND ATOPY IN WORKERS WITH AN EPOXY ADHESIVE

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Summary

Seven workers using an epoxy adhesive cured with pyromellitic dianhydride were studied. Workers both mixed and used the adhesive. Each completed a questionnaire about previous respiratory symptoms, family or personal history of atopy, smoking history and symptoms using the adhesive. FEV_1 was measured as a base-line and after working with the adhesive. Skin tests to common allergens were performed on all subjects. Two subjects who stated they wheezed with adhesive had falls in FEV_1 of 15% and 18% from base-line. Totally symptom-free subjects had falls of less than 4% from base-line or a rise in FEV_1. There was no clear relationship between smoking habits or atopic state or skin rashes with resin and a fall in FEV_1. There is no simple way to identify those at risk of developing wheeze. Care should be taken with epoxy adhesives to avoid sensitization and where it occurs a simple questionnaire would provide a screening method.

INTRODUCTION

Epoxy resins are long-chain polymers formed from epichlorhydrin and bisphenol A. They are used extensively as adhesives and in plastics. Hardening is by the addition of a curing agent, either with acid anhydrides and application of external heat or with cold curing with amine compounds.

Contact dermatitis occurs quite frequently with exposure to epoxy resins (Rycroft & Calnan 1976). Respiratory symptoms after exposure to epoxy resins (Mehl et al. 1967; Gul'ke 1971; Sargent & Mitchell 1976; Chester et al. 1977; Fawcett et al. 1977) are perhaps less common.

One patient presented at our chest clinic with symptoms she attributed to the adhesive she used at her factory, and she was studied with all her workmates. In this paper we report results of respiratory function tests in the seven subjects working with the adhesive (Eccobond 104) in relation to their symptoms and atopic state.

Materials and Methods

Industrial process

Up to six women workers and a male supervisor worked in a room of approximately 5 × 2.5 × 3 m. The temperature of the room was maintained at 15–20°C by central heating and an electric heater with a thermostat at the time when our patient developed symptoms. Adhesive components were weighed in one corner of the room and 5 g resin and 3.2 g pyromellitic anhydride powder were then mixed manually with a small spatula. Once mixed, the container of adhesive was placed in a vacuum extractor for ten minutes to remove bubbles; this evacuated directly into room air. The container of adhesive was placed on a work bench near the worker, who used it to glue pieces of ceramic as small as 3 mm long on to transducers. Once these were in place, the adhesive was cured for two hours at 180°C in an oven also in the room; a vent in the oven opened into room air. Once cured, hot transducers were placed on the work bench and allowed to cool. Two further stages of glueing and curing followed.

After complaints from workers the weighing and mixing were done by the supervisor in a separate area. This change had already been made when investigations were done.

The supervisor wore disposable gloves for the procedure of weighing and mixing and avoided shaking the pyromellitic anhydride powder into the air. The workers stated that when they had mixed the glue they had never worn gloves, had not washed their hands after mixing and had often had direct skin contact with the powder and shaken more of it into the air.

Method

Respiratory function tests were conducted in the workroom using a McDermott spirometer. FEV_1 and FVC were measured three times and a mean FEV_1 and FVC calculated on each occasion. Base-line readings were taken in the morning and repeated after 30 minutes. A mean of these base-line readings was calculated and subsequent readings were expressed as a percentage of it. FEV_1 and FVC were repeated at intervals of ten, 20, 30, 60 and 120 minutes after exposure to mixed adhesive. Subject 1 was re-tested after she had inhaled cromoglycate 20 mg at 20.30 hours the previous evening and 06.00 hours on the morning of the test with exposure to adhesive occurring at 10.00 hours. Three subjects, two of whom had symptoms on mixing the adhesive, were also tested after mixing the epoxy resin with acid anhydride.

All seven subjects answered a questionnaire. This included criteria for cough and sputum as in the Medical Research Council's Questionnaire (MRC 1966) and criteria for grades of dyspnoea (Cotes 1975). Details of smoking habits, personal or family history of atopy, and any symptoms from using the adhesive and their precise timing were recorded. Details of concurrent illness or therapy were asked for and any exposure to epoxy resins in previous employment.

All subjects had prick tests to five common allergens; house dust, *D. pteronyssinus*, grass pollen, horse, *Aspergillus*, and formol saline control (Bencard).

RESULTS

Previous health

None of the seven subjects had hay fever or asthma or wheeze before using the adhesive. None had dyspnoea on exertion or chronic bronchitis.

Reactions to adhesive

Results are summarized in Table I.

The questionnaire revealed that two subjects who had noticed nasal symptoms and wheeze whilst using the adhesive both had much more severe symptoms when mixing it. The subject who had attended chest clinic (Subject 1) had a maximum fall in FEV_1 of 15% with severe rhinorrhoea ten minutes after exposure to mixed adhesive (Fig. 1). After inhaled cromoglycate there was a fall in FEV_1 of 12% at 20 minutes, suggesting little benefit from its use. She did not wish to be tested when mixing the adhesive since this had caused such severe symptoms in the past. She had often been sent home from work because of wheeze but recovered rapidly.

Subject 2 said that her wheeze was worst at 90 minutes but continued into the evening, and in the past had increased during the week until finally she had been away from work for eight days with 'bronchitis', returning to another part of the factory. FEV_1 fell by 9.4% at 60 minutes using mixed adhesive, and by 18% at 120 minutes after mixing the

Table I. Characteristics of subjects and their response to epoxy adhesive

	Subject						
	1	2	3	4	5	6	7
Using mixed adhesive							
Nasal symptoms	+	+	—	+	—	—	—
Respiratory symptoms	+	+	—	—	—	—	—
Time of wheeze (min)	45	90	—	—	—	—	—
Fall in FEV_1 (%)	15	9	7	3	none	none	—
Time of fall (min)	10	60	30	60	—	—	—
Mixing adhesive							
Fall in FEV_1 (%)		18		2			1
Time of fall (min)		120		10			35
Atopy							
Subject		nickel	—	+	—	—	—
Relative	—	+	+	—	—	—	+
Prick test	—	—	+	—	—	—	—
Cigarettes (No./day)	0	5	0	<1	3	15	15
Duration of exposure (months)	12	7	18	12	12	1¼	12
Original FEV_1 (litres)	1.97	2.83	2.87	3.78	2.33	2.89	4.86

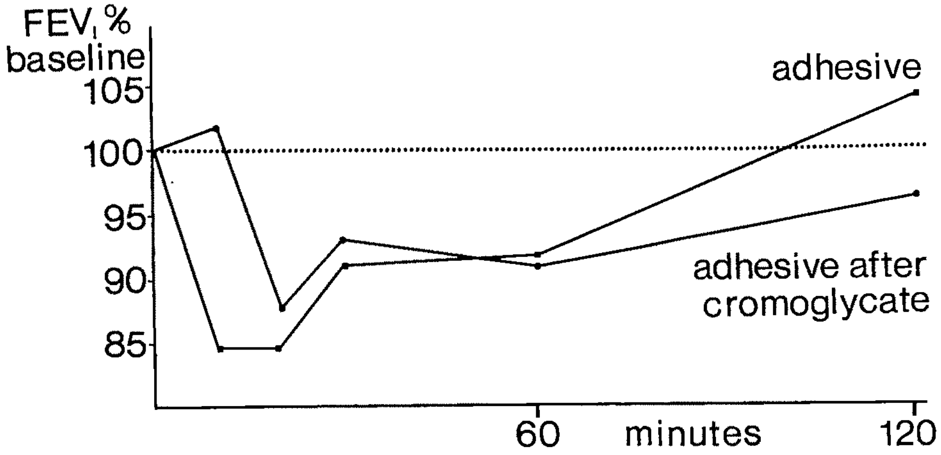

Fig. 1. Subject 1. Change in FEV_1 as percentage of base-line value

components (Fig. 2). She had noticed nickel sensitivity in the past and a maternal cousin had asthma.

Subject 3 had noticed no wheeze with the adhesive, but had skin irritation after contact with the powder. Her FEV_1 fell by 7% at 30 minutes. She had a positive prick test to *D. pteronyssinus*, and her sister and aunt had asthma.

Subject 4 had a history of nasal symptoms on direct contact with the anhydride and

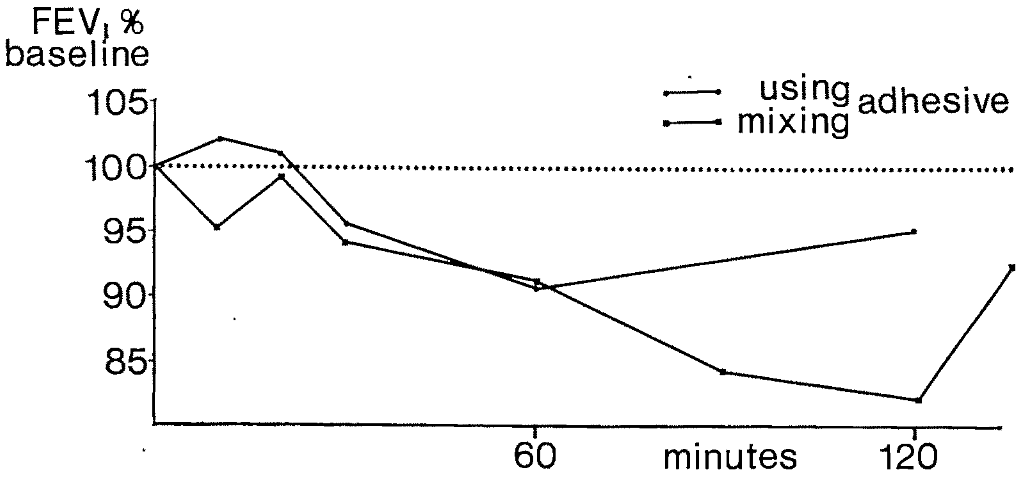

Fig. 2. Subject 2. Change in FEV$_1$ as percentage of base-line value

had also had skin rashes with it requiring treatment with topical hydrocortisone. There was no change in FEV$_1$ even after mixing the adhesive.

Changes in FVC did not exceed 7.6%.

Duration of exposure

There was no significant difference in the duration of exposure in those who developed wheeze and those who did not.

Smoking habits

There was no association of symptoms with numbers of cigarettes smoked; the most severely affected subject was a non-smoker.

Atopic history

Both affected and unaffected subjects had relatives with asthma. The two subjects who wheezed had skin allergy to nickel (Subject 2) and urticaria after eating peaches (Subject 1) and one other subject (3) was sensitive to some soaps and insect bites.

DISCUSSION

There is an increasing appreciation that asthma can be precipitated by epoxy resin systems. Gul'ke (1971) found wheezing in 70 of 488 (14.3%) workers with an epoxy resin system. Sargent and Mitchell (1976) found complaints of wheeze in four of 15 workers with an amine epoxy resin system and significant fall in FEV$_1$ in all heavily exposed. No relationship to atopy was sought in either group. Fawcett et al. (1977) described five subjects with falls in FEV$_1$ after exposure to epoxy resin systems, four with acid anhydrides. Two of the four had no positive prick test or history of atopy; one had previous asthma and one other had wheezed. Two other subjects with positive prick tests to common allergens were found to have no significant fall in FEV$_1$. No clear pattern emerges of atopic subjects being particularly likely to be sensitized. This matches our findings; the only subject with a clear atopic history did not wheeze and those with a family history of atopy were represented both in sensitized and non-sensitized groups.

The development of a skin rash does not indicate sensitization which proceeds to cause wheezing; our subject who had skin rashes developed no wheeze despite further exposure, whilst the subject who wheezed had no skin rashes whatever.

Both immediate and non-immediate asthmatic reactions have been reported (Chester et al. 1977; Fawcett et al. 1977). We found one example of an immediate reaction, with the maximum fall in FEV_1 at ten minutes and a history of rapid recovery. There was also one example of a fall in FEV_1 starting at 30 minutes and at a maximum at two hours (Fig. 3). The subject gave a history of symptoms which were severe some hours after work, suggesting a late reaction.

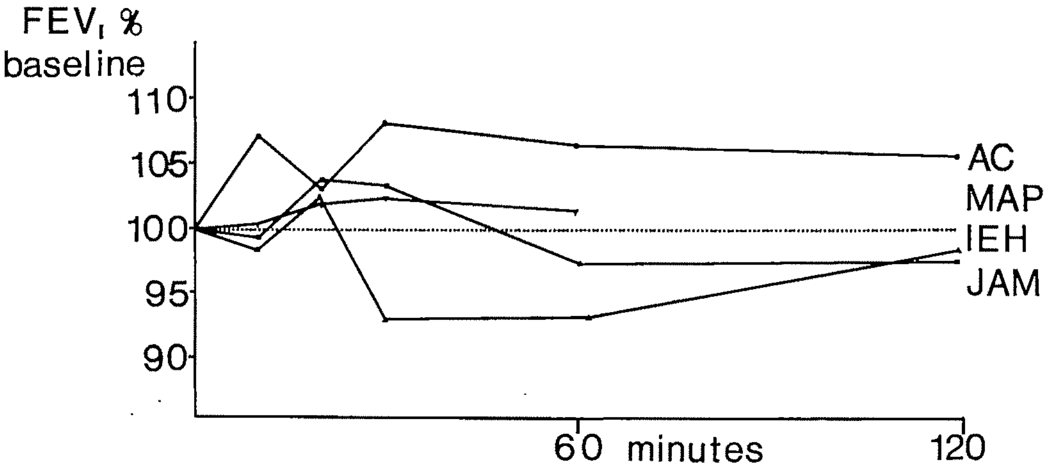

Fig. 3. Change in FEV_1 as percentage of base-line value in asymptomatic subjects using adhesive

Cromoglycate in the patients' usual dosage (20 mg night and morning) did not prevent the immediate asthmatic response. This finding agrees with that of Chester et al. (1977).

There was no evidence for cigarette smoking predisposing to wheeze; our sensitized subjects included two non-smokers. Sargent and Mitchell (1976) suggested that smokers should not work in an area where there is exposure to resin, which would be an unproven precaution with the resin system we studied.

The likelihood of wheezing developing does not depend only on duration of exposure. Our sensitized subjects had an exposure of seven to 12 months, as did three of four non-sensitized subjects. Fawcett et al. (1977) found sensitization after exposure of five to 12 months, whilst another subject exposed for eight years did not become sensitized. Sensitization has developed for the first time after 18 years exposure to a phthalic acid system (Chester et al. 1977). It would seem that sensitization is most likely to occur in the first year but may occur at any time thereafter.

Our questionnaire was extremely valuable in assessing subjects. Those complaining of wheeze at work had a fall of FEV_1 of 9% to 18% and those who did not have wheeze had falls in FEV_1 of 7% or less, all but one of less than 3%. The expected timing of symptoms correlated well. A questionnaire might provide a simple non-invasive method

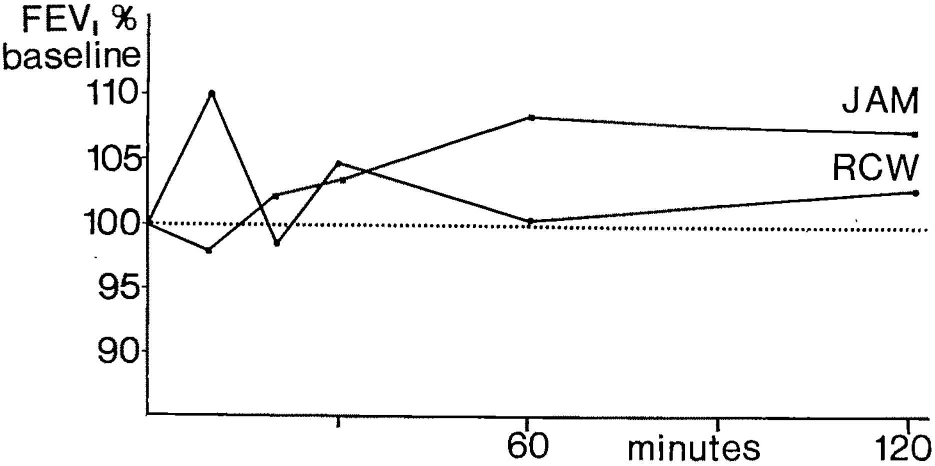

Fig. 4. Change in FEV$_1$ as percentage of base-line value in asymptomatic subjects mixing components of adhesive

of selecting sensitized subjects and findings could be confirmed by further investigations.

Greater awareness of the respiratory effects of epoxy resin systems can lead to greater care in their handling and reduce the risk to individuals. Instructions accompanying this resin stated that it should be used only with adequate ventilation and that prolonged or repeated breathing of vapour should be avoided. The manufacturers told us that they would suggest the use of a fume cupboard for mixing the two components, and this was subsequently installed, and the curing and vacuum extraction moved to a room away from the workers, with improvements in their symptoms. This would seem to offer more hope for prevention of epoxy resin asthma than any screening of workers for atopy or smoking history before exposure.

ACKNOWLEDGEMENTS

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RESPONSE OF THE LUNG AIRWAY TO EXERCISE TESTING IN ASTHMA AND RHINITIS

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Summary

The reactivity of the large and small airways of the lung in a group of ten atopic subjects with rhinitis was compared with that in ten non-atopic control subjects and in 17 with atopic asthma. Atopic state was assessed by skin prick testing with 22 common allergens and by measurement of total serum immunoglobulin E (IgE) antibody. The atopic state of the rhinitis and asthma patients was similar. Exercise provocation tests were performed on each subject and changes in airway function were measured by peak expiratory flow rate, forced expiratory volume in one second, vital capacity, maximal expiratory flow volume curves and closing volume. There were no statistically significant differences between the changes in lung function after exercise in the rhinitis patients compared with the controls. There were, however, statistically significant changes in all the measurements of respiratory function in those with asthma compared with the other two groups. The falls in forced expiratory flow rates in the asthmatic subjects were greater at lower lung volumes than near to total lung capacity, perhaps indicating that narrowing of small, as well as large, airways was occurring. No correlation was found between the magnitude of the airway response to exercise and either the total serum IgE antibody or the mean weal diameter of positive skin tests in each subject. Atopic subjects with rhinitis but not asthma showed no evidence of bronchial hyper-reactivity on exercise testing. It is therefore suggested that single exercise provocation test can discriminate subjects with atopic asthma from those with other atopic disorders.

INTRODUCTION

The increased reactivity of the airway of the lung in patients with asthma has been recognized for many years (Willis 1679). It can be demonstrated by a variety of stimuli including exercise (Floyer 1698; Godfrey 1975), exposure to cold air (Wells et al. 1969), inhalation of histamine (Curry 1946) and of cholinergic drugs (Dubois & Dautrebande 1958). In addition, there have been reports that some patients with allergic rhinitis, rather than asthma, show increased airway reactivity after the inhalation of acetyl-beta-methylcholine (methacholine) (Townley et al. 1965). The evidence from studies with methacholine is conflicting about both the magnitude and the nature of the airflow obstruction in the lungs of patients with rhinitis. Townley et al. (1975*b*) showed a greater than 20% fall in the forced expiratory volume in one second (FEV_1) in over half the patients with allergic rhinitis that they studied. On the other hand, Fish et al. (1976)

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found no significant changes in FEV_1 in allergic rhinitic patients after methacholine inhalation when compared with control subjects. They did find significant alterations in specific airway conductance (SGaw) and interpreted this as an indication of changes in the large airways of their rhinitic subjects. Grossman and Putman (1975) measured maximal mid-expiratory flow rates (MMEF), maximal terminal flow and FEV_1 after methacholine inhalation. They found changes which they interpreted as predominantly of small airway function in their patients with allergic rhinitis.

Although partial blockade of beta-adrenergic receptors (Szentivanyi 1971) or even increased alpha-adrenergic receptor activity (Patel & Kerr 1973) has been suggested as the mechanism of the bronchial hyper-reactivity, the fundamental abnormality remains unknown. Patterson et al. (1965) and Fink and Schleuter (1969) showed that the bronchial response of experimental animals to methacholine could be enhanced by passive sensitization with immunoglobulin E (IgE). This suggests a possible role for this antibody in the aetiology of increased airway reactivity. Further, bronchial hyper-reactivity has been demonstrated after methacholine inhalations in some subjects who had neither asthma nor hay fever, but who did show positive skin tests to common allergens (Townley et al. 1975*b*).

The purpose of this investigation was to study the airway responses of atopic patients with rhinitis and asthma by exercise testing rather than by inhalation of pharmacological agents. Alterations in large airway function were assessed by measurement of forced expiratory flow rates at high lung volume, and changes in small airways were assessed by measurement of forced expiratory flow rates at low lung volume and closing volumes (CV). The airway responses were correlated with the atopic state of the subject indicated by the number and weal diameter of positive skin prick tests to common allergens and by the total serum levels of IgE antibody.

Materials and Methods

Subjects. All subjects were male and aged between 20 and 37 years. Ten non-atopic control subjects, ten atopic subjects with rhinitis and 17 subjects with atopic asthma were studied (Table I).

Clinical history. All the histories were taken by the same investigator. The control subjects had no past or present history of rhinitis (seasonal or perennial attacks of sneezing, running or blockage of the nose), wheezing or asthma. The subjects with rhinitis were questioned exhaustively to ensure that they had never experienced episodes of wheezing. Uncertainty about a past history of wheezing in rhinitic subjects excluded them from the study. All the rhinitics had had symptoms in the year before investigation. All the patients with asthma had experienced attacks of wheezing within a year of the study and the majority also had rhinitis. There was no significant difference between the number of subjects in each group who were cigarette smokers (Table I).

Atopic state and serum IgE antibody. The atopic state of each individual was determined by skin prick testing with the following 22 common inhalant and food allergens (the concentrations are expressed in terms of weight to volume): house dust 150%, *Dermatophagoides pteronyssinus* 1.2%, grass pollens (B2) 2.5%, shrub pollens (B1) 2.5%, tree pollens (B3) 2.5%, cat fur 150%, dog hair 150%, feathers 150%, horse hair and danders 150%, milk 10%, wheat 10%, fish 10%, nuts 10%, whole egg 5%, *Alternaria tenius* 5%, *Aspergillus fumigatus* 10%, *Aspergillus terreus* 10%, *Cladosporium herbarum* 10%, *Merulius lacrymans* 10%, *Sporobolomyces roseus* 5%, yeast 10%, *Candida albicans* 10%.

Both the number and the weal diameter of the positive reactions were recorded 20 minutes after the skin prick test. Weals of 1 mm or more in diameter after allergen testing were considered positive provided that there was no wealing reaction to the control skin test. None of the subjects took any medication in the 24 hours before skin testing. The presence of one or more positive skin tests was considered evidence of atopy (Pepys 1975). All the patients with rhinitis and asthma had positive skin reactions to one or more of the allergens used, placing them into the atopic group. None of the control subjects showed such reactions (Table I).

Serum was taken at the time of skin testing. IgE antibody was measured using a solid-phase radio-immunosorbent test (Pharmacia Ltd, Uppsala, Sweden) modified according to the technique of Wide (1971) to improve the sensitivity of the method for lower serum levels of the antibody (< 100 IU/ml).

Exercise testing. The technique used for exercise testing was that of free-range running. Each subject ran along a flat corridor for six to eight minutes until a pulse rate of 160 beats per minute was achieved. This method and duration of exercise testing has been shown to produce the maximum change in airway function (Godfrey 1975). Base-line measurements of respiratory function were made on each subject after the clinical history had been elicited and skin testing performed. The subjects were exercised and the airway response measured immediately after cessation of exercise and at ten-minute intervals for the next 30 minutes. No subject received any medication in the 24 hours before the exercise test. After completion of the exercise tests and measurements of respiratory function, each subject inhaled 200 μg of salbutamol. Respiratory function tests were repeated. Falls in peak expiratory flow rate (PEFR) greater than 10% from base-line were considered positive exercise tests (Pierson 1969; Silverman & Anderson 1972).

Table I. Characteristics of the study groups

	Non-atopic control ($n = 10$)	*Atopic rhinitis* ($n = 10$)	*Atopic asthma* ($n = 17$)
Age (years, mean ± SD)	29 ± 3	27 ± 5	28 ± 5
Past history			
Rhinitis	0	10	12
Asthma	0	0	17
Current history			
Rhinitis	0	10	12
Asthma	0	0	17
Positive skin prick test	0	10	17
Cigarette smokers	5	4	7

The measurements of respiratory function performed before and after exercise testing were PEFR, FEV_1, VC, maximal expiratory flow volume curves (MEFV curves), and CV. Maximal expiratory flow rates at 75, 50 and 25% of vital capacity (Vmax_{75}, Vmax_{50} and Vmax_{25}) were measured from the MEFV curves. PEFR was measured by the Wright peak flow meter. Forced expiratory spirograms and MEFV curves were obtained simultaneously from a Fleisch pneumotachograph whose inlet and exit cones were extended to minimize axial streaming. The pneumotachograph output was conducted through a stable integrator from which volume signals were obtained, and the curves displayed on a storage oscilloscope. Flow calibration was obtained from air rotameters and volume from a syringe graduated to 5 litres by water displacement. Volume measurements were independent of flow to 10 litres/second. CV was measured by the nitrogen washout technique (Anthonisen et al. 1969) using an Ohio 700 nitrogen analyser with a response time of 50 msec in a circuit utilizing the pneumotachograph and integrator linked to the storage oscilloscope. All oscilloscope traces were recorded permanently by Polaroid photography. Three control traces were obtained from each subject after a period of training. The CV from each trace was measured by two observers and the mean calculated. The subdivisions of lung volume were measured before exercise testing by helium dilution using a Godart expirograph with linked functional residual capacity (FRC) computer (Cotes 1965). All volumes were corrected to BTPS.

RESULTS

Skin prick tests and total serum IgE antibody

The results of skin testing and measurement of IgE antibody are shown in Table II. The control subjects had no positive reactions to skin testing, and the geometric mean and standard deviation (SD) of their total serum IgE antibody was 40 ± 112 units/ml. All the subjects with rhinitis showed one or more positive reactions on skin testing, as did those with asthma. The mean (± SD) number of positive skin reactions together was 8.1 ± 4.6 in those with rhinitis and 8.3 ± 3.6 in those with asthma. The weal diameter of these reactions in the two groups was 5.3 ± 2.6 mm and 5.2 ± 1.6 mm respectively (mean ± SD). The geometric mean (± SD) of the total serum IgE antibody was 422^{+765}_{-277} units/ml in the rhinitis group, and 381^{+689}_{-243} units/ml in the subjects with asthma. The clinical history together with the results of skin testing indicated that grass pollen and the house dust mite were the important allergens in the development of disease in the atopic subjects.

Table II. Results (mean ± SD) of skin prick testing and measurement of serum IgE antibody

	Non-atopic control ($n = 10$)	*Atopic rhinitis* ($n = 10$)	*Atopic asthma* ($n = 17$)
Positive skin tests	0	8.1 ± 4.6	8.3 ± 3.6
Weal diameter (mm)		5.3 ± 2.6	5.2 ± 1.6
Total serum IgE (IU/ml)	40^{+122}_{-30}	422^{+765}_{-277}	381^{+689}_{-243}

Respiratory function tests

Before exercise. Table III summarizes the respiratory function of the three groups before exercise testing. The results were calculated as a percentage of the predicted values (Cotes 1965; Lapp & Hyatt 1967; Buist & Ross 1973) for each subject, and shown in Table III as the mean ± SD for each group. The only significant differences on testing were reduction in FEV_1, PEFR, $Vmax_{75}$ and $Vmax_{50}$ in the subjects with asthma compared with the control group ($P < 0.025$).

After exercise. The changes in the measurements of respiratory function induced by exercise are shown in Table IV. The values given are the mean ± SD of the maximum changes for each of the subjects in the three groups from the measurements before exercise. No significant changes were detected in respiratory function between the non-atopic control group and the atopic group with rhinitis and none of these subjects had a positive exercise test. The changes in all the measurements of respiratory function which occurred after exercise testing in the asthmatic group were significantly different from those occurring in the control group ($P < 0.02$). Eleven of these 17 subjects showed positive exercise tests. FEV_1 and, to a lesser degree, VC were reduced in the asthma group after exercise. The reduction in forced expiratory flow rates in this group was least at high lung volumes, namely PEFR, and increased as the lung volume decreased, the greatest falls occurring in Vmax$_{50}$ and Vmax$_{25}$. It was possible to obtain readings from the closing volume traces despite increase in the gradient of phase III which usually occurred. Discrepancies between the values obtained by the two observers were small. Closing volume measurements showed mean falls in the control and rhinitis group and a mean rise in the asthmatic subjects.

Table III. Results of respiratory function tests before exercise

Test	*Non-atopic control* (*n*=10)	*Atopic rhinitis* (*n*=10)	*Atopic asthma* (*n*=17)
FEV$_1$	103±8	97±15	88±26†
VC	112±8	106+16	107±16
RV	103±28	106±24	139±50
TLC	109±10	106±16	115±15
FRC	108±17	107±17	123±26
PEFR	102±8	97±9	85±20*
Vmax$_{75}$	94±18	103±27	70±24†
Vmax$_{50}$	83±26	100±36	60±24‡
Vmax$_{25}$	85±19	95±35	72±28
CV/VC	111±19	101±30	120±33

Results expressed as mean ±SD for the group, as a percentage of the predicted value. Significant differences from the control: *$P<0.01$; †$P<0.025$; ‡$P<0.05$.

Table IV. Changes in respiratory function tests after exercise

Test	*Non-atopic control* (*n*=10)	*Atopic rhinitis* (*n*=10)	*Atopic asthma* (*n*=17)
FEV$_1$	1±3	−2±2	−18±11*
FVC	0±4	−2±4	−8±5†
PEFR	−3±5	−3±2	−19±11*
Vmax$_{75}$	2±7	0±7	−27±18*
Vmax$_{50}$	0±12	−3±11	−32±16*
Vmax$_{25}$	1±13	4±18	−31±23*
CV/VC	−15±19	−7±19	16±34‡

Results expressed as the mean ±SD of the maximum percentage change for each subject. Significant differences from the control: *$P<0.01$; †$P<0.025$; ‡$P<0.05$.

Airway response to exercise and atopic state

The weal diameter of the positive skin prick tests and the levels of total serum IgE antibody were closely similar in the subjects with rhinitis when compared with those with asthma. Both groups differed significantly in atopic state from the control subjects (Table II). Whilst the subjects with asthma showed marked bronchial hyper-reactivity on exercise testing, those with rhinitis did not. (Table IV). Fig. 1 shows the relationship between the maximum percentage change in FEV_1 induced by exercise and the level of total serum IgE antibody in the serum of each subject. No significant correlation occurred between these variables either when all the subjects were included (Fig. 1) or when the atopic subjects were considered alone.

The same results were obtained when the other measurements of respiratory function were compared either with total levels of serum IgE antibody or the mean weal diameter of the positive skin tests in each subject.

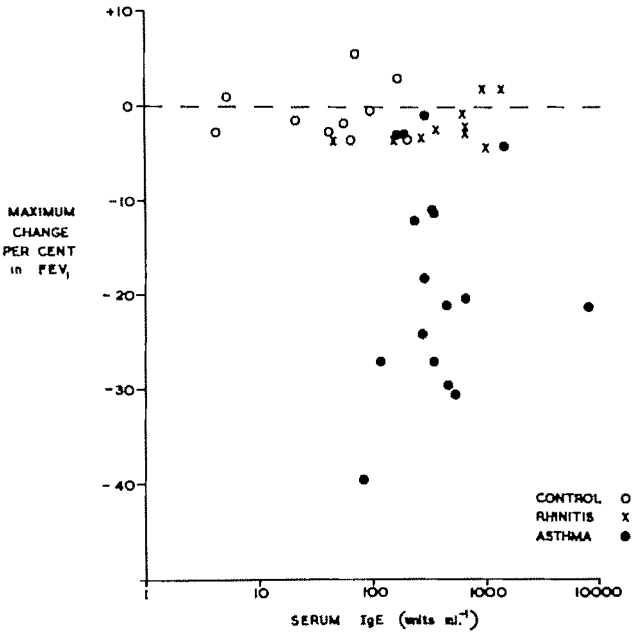

Fig. 1. The relationship between the maximum percentage change in FEV_1 after exercise and the level of total serum IgE antibody in control subjects and those with atopic asthma and atopic rhinitis

Discussion

In this study we investigated the changes induced in the lung airway by a single exercise test in non-atopic control subjects and in those with atopic rhinitis and atopic asthma. Comparison of results in the rhinitis group with those in control subjects showed close similarity and neither the mean values for the group nor those for individual subjects showed evidence of airflow obstruction after the exercise test. In contrast, there were significant falls after exercise in the mean values of all measurements made during forced expiration in the asthma group. However, in six of the 17 subjects with asthma, the PEFR fell by less than 10% and in four of these the FEV_1 also decreased by less than 10%. The incidence (65%) of positive tests after a single period of exercise in our group of asthmatic subjects was similar to that found by Godfrey (1974). From this study it is clear that a single exercise test does not induce airflow obstruction in subjects with atopic rhinitis.

Airflow obstruction after inhalation of pharmacological agents has been demonstrated in subjects with rhinitis by a number of investigators (Grossman & Putnam 1975; Townley et al. 1975*a*, *b*; Fish et al. 1976). This difference from our results requires explanation. Inhalation of methacholine has been shown to induce significant airflow obstruction in control subjects who have neither rhinitis nor asthma (Grossman & Putnam 1975; Townley et al. 1975*b*). Townley et al. (1965) showed that eight of 14 hay fever subjects developed falls in FEV_1 of greater than 15% after inhalation of methacholine, but seven were shown to have asthma when they inhaled specific allergens. In our study we took particular care to exclude patients who were in any doubt about a past or present history of wheezing. Such variability in selection of patients may also account partly for the finding of positive exercise tests in children with rhinitis. In the study by Jones (1966) some of the children had significant reductions in FEV_1 before testing. Further, Jones incorporated the airway response to bronchodilators in his assessment of airway changes, the results being expressed as the Jones Lability Index. In our study, both the control and rhinitis subjects showed an equal and marked response to bronchodilators, but insignificant airflow reduction after exercise testing. In our control subjects the FEV_1 fell by $1 \pm 3\%$ after exercise, but the Jones Lability Index calculated from changes in FEV_1 was $8 \pm 4\%$ (mean ± SD). In the rhinitis group the FEV_1 fell by $2 \pm 2\%$ after exercise while the Jones Index was $9 \pm 3\%$ (mean ± SD). This emphasizes the disproportionate contribution of the bronchodilator response to the total airway lability in non-asthmatic subjects.

The asthmatic subjects in our study showed reductions in maximal expiratory flow rates not only at high but even more at low lung volumes after exercise.

Reduction of flows at high volumes, as well as in PEF, suggest involvement of large airways. The reduction of flows at low volumes, with increases in closing volume and the gradient of phase III, are evidence of small airways constriction occurring also. This is consistent with the findings of Benetar and König (1974) that the small airways were predominently affected in asthmatic children, on the basis of responses to breathing helium mixtures. Their findings were not confirmed in adults by Mildon et al. (1974) also using helium mixtures. The interpretation of the effects of breathing low density gas mixtures is now, however, believed to be more complex than originally conceived (Lisboa et al. 1980).

The changes demonstrated in pharmacologically induced asthma show a similar pattern. Grossman and Putnam (1975) found changes in MEFV curves after methacholine inhalation in asthmatic subjects which were similar to those found in this study and suggested that the small airways were involved. Fish et al. (1976) found that FEV_1 and SGaw were reduced in their study of pharmacologically induced asthma and suggested that constriction of both large and small airways was occurring.

We have reported similar changes after allergen challenge (Green et al. 1976). It appears that the bronchial tree is affected throughout its ramifications during asthma induced both by pharmacological agents and by exercise.

In our study we were unable to find any relationship between atopic state and the presence of bronchial hyper-reactivity on exercise testing. Further, there was no correlation between the degree of exercise-induced airflow obstruction and the total serum levels of IgE antibody or the mean diameter of the positive skin tests to common allergens. These findings are in accord with those of Bryant and Burns (1976) who used inhalation of histamine to demonstrate bronchial hyper-reactivity in asthmatic subjects. The lack of any demonstrable relationship in our study between skin test results and bronchial reactivity is consistent with the work of Silverman and Turner-Warwick (1972) who found increased airway reactivity on exercise testing in asthmatic patients who were skin test negative. Nevertheless, this evidence does not exclude a role for IgE antibody in the development of bronchial hyper-reactivity. A relevant factor in this phenomenon may be the amount or affinity of IgE antibody present on mast cells in the respiratory tract, rather than that present in serum or on the mast cells in the skin. While it is possible to determine the amount of IgE in serum and skin with relative ease, the amount present on mast cells in the respiratory tract is much harder to measure. The relationship between the quantities of this antibody at these different sites remains to be accurately defined (Assem et al. 1971; Ishizaka et al. 1973).

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FIBRINOGEN DEGRADATION PRODUCTS IN PLEURAL EFFUSIONS

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Summary

This study investigates the diagnostic value of fibrinogen degradation products (FDP) in pleural fluid and serum. Thirty patients with pleural effusions due to a variety of causes were investigated.

The concentration of FDP in pleural fluid was significantly higher in patients with malignancy, infection and pulmonary embolus than in patients with congestive cardiac failure. The concentration of FDP in serum was not significantly different between any of the groups.

We conclude that estimation of the concentration of FDP in pleural fluid, a simple biochemical procedure, has some value in differential diagnosis of pleural effusion and complements existing tests.

INTRODUCTION

Pleural effusion is a common clinical condition, but the underlying cause may be difficult to confirm. History and clinical examination usually provide valuable clues to the aetiology of an effusion. Pleural biopsy and biochemical and cytological studies of the pleural fluid provide further diagnostic information. Measurement of lactate dehydrogenase and its isoenzymes in serum and pleural fluid may help in the differentiation of malignant from benign exudative effusions (Light & Ball 1973; Fröhlich & Keller 1967). Protein concentration may help in differentiation between a transudate or exudate, using a concentration of 30 g/litre as the dividing line (Chandrasekhar & Buehler 1974). Light et al. (1972) made this test more sensitive by calculating the pleural fluid to serum protein ratio; values greater than 0.5 indicated exudation and lower values transudation. Diuretic therapy may increase the pleural fluid protein, giving a false impression of an exudate (Pillay 1965).

This study was designed to investigate the value of measurement of fibrinogen degradation products in serum and in pleural fluid in the differential diagnosis of pleural effusion. FDP concentration has been shown to have diagnostic value in other body fluids. Purdie et al. (1975) have shown raised FDP concentrations in amniotic fluid where fetal neural tube anomalies were present. The value of estimation of serum FDP in thromboembolic diseases has been widely studied (Gurewich et al. 1973; Bynum et al. 1976; Vasilescu et al. 1976; Cade et al. 1975).

Fibrinogen concentration in pleural fluid was studied by Glauser et al. (1975) but not used as a diagnostic tool; they suggested that fibrinolysis may have accounted for their variable results. Our study avoids this difficulty by measuring the products of fibrinogen degradation.

Patients and Methods

Thirty patients with pleural effusions admitted to Harrogate hospitals between January 1977 and July 1978 were studied. They were placed in four main groups according to the aetiology of their effusion: (1) pulmonary embolus, (2) congestive cardiac failure, (3) infection, and (4) malignancy. There were also some patients who did not fit into any of these groups. The diagnosis of pulmonary embolus was made on radiographic, electrocardiographic and radio-isotopic evidence. Congestive cardiac failure was diagnosed on clinical and radiographic evidence. Chest infection was diagnosed on clinical, radiographical and bacteriological evidence. The diagnosis of malignancy was made on clinical grounds and confirmed by histological study of bronchoscopic or cytological samples. Patients were excluded if they fitted more than one group.

After radiographic confirmation of the presence of an effusion, 2 ml of pleural fluid were aspirated and 2 ml of venous blood were taken at the same time. Both these specimens were injected into Wellcotest FDP tubes and refrigerated until ready for analysis by the Wellcotest latex screening method (Garvey & Black 1972). The cause of the effusion in each case was not revealed to the laboratory staff.

RESULTS

Of the 30 patients six had pulmonary embolus, five congestive cardiac failure, five chest infection, 11 malignancy, one systemic lupus erythematosus (satisfying the American Rheumatism Association criteria), one cirrhosis with hypoalbuminaemia and in one patient the final diagnosis is still uncertain. In the malignancy group, eight had primary bronchial carcinoma, one mesothelioma, one non-Hodgkin's lymphoma and one hypernephroma. The results of the FDP assays in pleural fluid and serum are shown in Fig. 1. The differences between the mean value in effusions due to congestive failure and in each of the other groups were statistically significant. However, the discrimination between effusions due to malignancy and to congestive failure was not absolute as two patients with malignant effusions had very low FDP concentrations.

The concentration of FDP in serum was lower than in the effusion in all patients except one in group one. There was no significant difference in the concentration of FDP in serum between any of the groups, but in no patient with congestive cardiac failure was the concentration greater than 2 μg/ml. There was no correlation between serum and pleural fluid concentrations of FDP.

The protein concentration in pleural fluid was measured in 11 of the 30 patients. The results are shown in Fig. 2. We were unable to demonstrate a significant correlation between pleural fluid protein content and FDP concentration ($r = 0.497$; $P > 0.1$).

DISCUSSION

These results show that FDP are present in a far greater concentration in pleural effusions due to malignancy, infection and pulmonary embolus than in congestive cardiac failure. The concentration of FDP reflects the degree of damage to pleural capillaries and lymphatics by inflammation or infarction. Plasma proteins, including fibrinogen, may be expected to leak out of damaged vessels in proportion to the extent of the inflammation or infarction; producing the raised concentrations found in malignancy, pulmonary embolus and infection. It is interesting to note that the pleural fluid protein concentration in the two patients with pulmonary embolus in whom it was measured was less than 30 g/litre and would therefore be labelled as a transudate. However FDP measurements distinguished these patients from those with congestive heart failure.

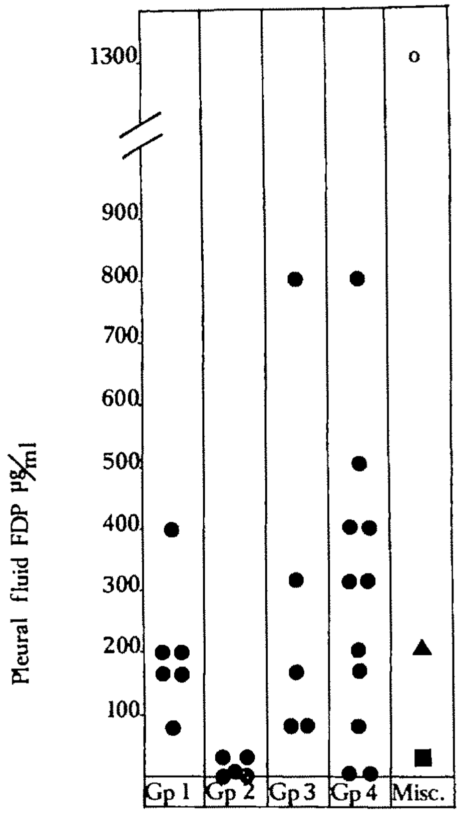

Fig. 1. Pleural fluid FDP concentration in all patients, grouped according to diagnosis. Group 1, pulmonary embolism, 200 ± 107 μg/ml; Group 2, congestive heart failure, 19 ± 20 μg/ml; Group 3, infective, 288 ± 302 μg/ml; Group 4, malignancy, 291 ± 236 μg/ml (mean ± SD). In the miscellaneous group ■ = liver cirrhosis, ▲ = systemic lupus erythematosus; ○ = undiagnosed

In our study the method of FDP assay may have been insufficiently sensitive to detect any possible change in serum FDP concentration in different diseases. Bynum et al. (1976) showed significant differences in serum FDP concentration between pulmonary embolus, normal and non-thrombeombolic pulmonary diseases using a tanned red cell haemagglutination inhibition immunoassay.

This study was restricted to patients with pleural effusions probably due to a single pathology, those with dual pathology being excluded. However, it is often difficult to determine whether there is an underlying malignancy or pulmonary embolus in a patient with cardiac failure, who has a pleural effusion. Our findings suggest that one should consider other possible causes for an effusion, if a high concentration of FDP is

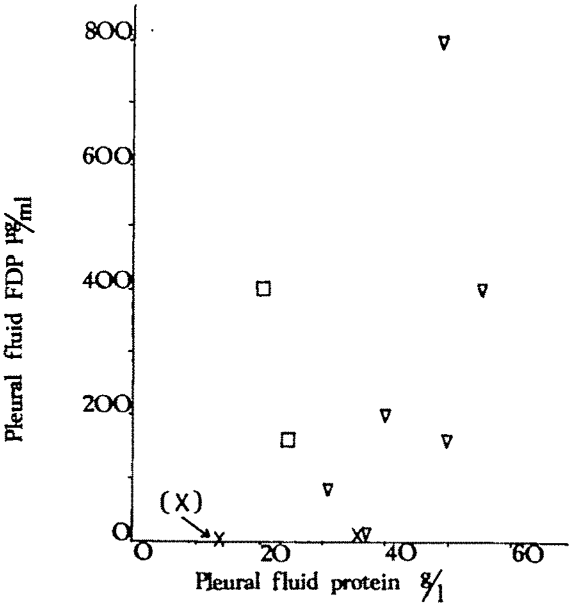

Fig. 2. Comparison of pleural fluid protein and FDP concentrations in eleven patients. □ = pulmonary embolus, × = congestive cardiac failure, ▽ = malignancy

found in a patient with heart failure, as none of our patients with heart failure had an FDP concentration greater than 40 µg/ml.

ACKNOWLEDGEMENTS

We would like to thank Dr S. J. Cameron, under whose care were most of the patients, for advice during the study and help in the preparation of the paper. We are grateful to Dr A. G. Stewart and Dr W. S. Suffern whose patients were included in the study, to Dr M. McEvoy and the staff of the Haematology department at Harrogate General Hospital and to Jane Wood for typing the manuscripts.

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AN EVALUATION OF CUSUM ANALYSIS IN ASTHMA

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Brompton Hospital, London

Summary

It has been claimed that cusum analysis may be a clearer way of expressing trends in serial peak flow (PF) measurements in asthma than visual inspection of peak flow charts. To assess this we have applied cusum analysis to serial PF measurements in patients receiving various forms of treatment for airflow obstruction. We found that cusum analysis usually gave no additional advantage over simple graphs of PF data. In cases in which trends were apparent only by cusum analysis, their dimension was such that they were unlikely to form the basis of decisions on treatment.

INTRODUCTION

Cumulative sum analyses can be applied to any series of measurements of one variable, and it has been claimed that they are of value in clinical medicine to discern trends in serial measurements which are obscured by their degree of scatter. A reference value is chosen and is subtracted from each subsequent measurement in a series. The differences are summed sequentially (i.e. cumulative sum analysis) and are plotted to expose trends in the mean serial data (see Appendix). Cusum analysis has been used in industrial quality control for many years and is employed in routine haematology and biochemistry laboratories to detect drifts in the base-line of serial measurements (Woodward & Goldsmith 1974). In clinical medicine, cusum analysis can be applied to temperature charts, blood pressure, serial haemoglobin or biochemistry measurements (Chaput de Saintonge & Vere 1974; Wohl 1977). Recently cusum techniques have been advocated for the interpretation of sequential peak flow data in patients with asthma and chronic bronchitis (Clarkson et al. 1978).

Methods

Twenty-seven consecutive patients with asthma or chronic obstructive bronchitis were studied during treatment in hospital. Seven patients were admitted with a diagnosis of chronic obstructive airways disease for intensive bronchodilator therapy, physiotherapy and a trial of oral corticosteroids. Ten patients were admitted for treatment of acute episodes of asthma, and ten patients were admitted for intensive treatment of chronic deteriorating asthma. In addition, seven normal subjects were studied before and during respiratory tract infections.

Cusums were derived from sequential PF measurements taken before and during periods of treatment. The mean of PF measurements before treatment provided the reference value from which all subsequent PF values during treatment were subtracted. These differences were sequentially summed to produce the cumulative sums and both serial PF measurements and derived cusum values were plotted graphically using a Prime 300 computer system. The vertical line on each figure indicates the start of treatment. The horizontal line intersecting it indicates the mean of pretreatment PF readings before treatment and also intersects the cusum plot at value zero, so that subsequent changes in cusum resulting from treatment may be more readily perceived. The vertical axis represents PF in litres per minute and the horizontal axis, time in days.

RESULTS

Of the seven patients with chronic obstructive airway disease, six showed improvement in serial PF measurements and a positive cusum slope: of these five also had symptomatic improvement. Fig. 1 is a representative example and shows the PF chart and derived cusum of one of these patients before and during treatment. The other patients who responded had similar graphs. Visual inspection of the PF chart shows obvious improvement and the cusum analysis reveals no additional information. It is interesting to note in this example that there was little change in PF readings until the tenth day of treatment when obvious improvement occurred, reflected by an upswing in the cusum line.

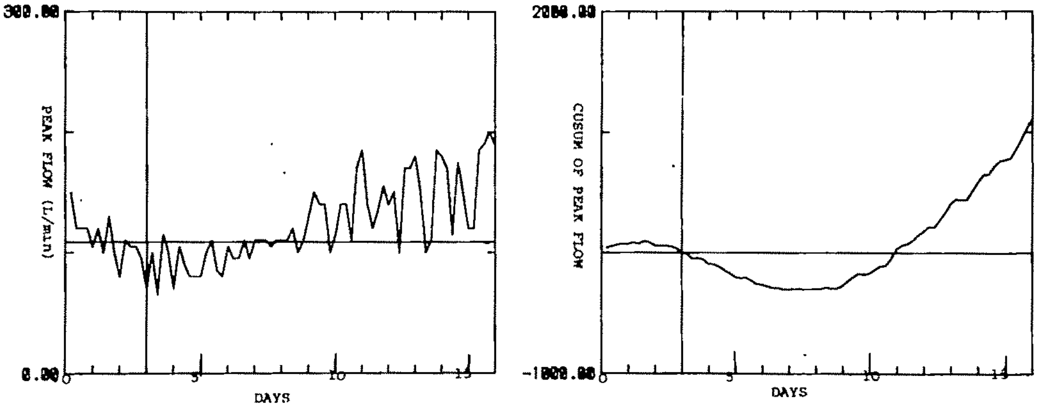

Fig. 1. Serial PF readings and derived cusum from a patient with chronic obstructive bronchitis who responded to treatment with oral corticosteroids

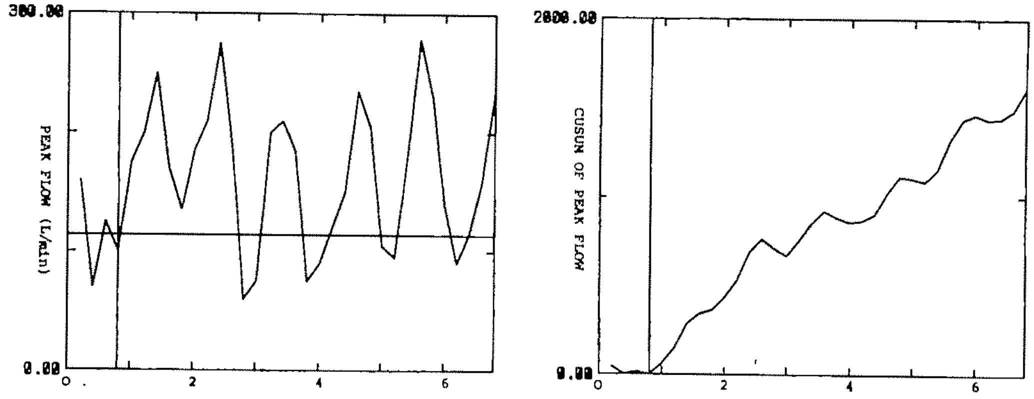

Fig. 2. PF readings and derived cusum of a patient admitted with acute asthma. The patient died unexpectedly after the last reading shown

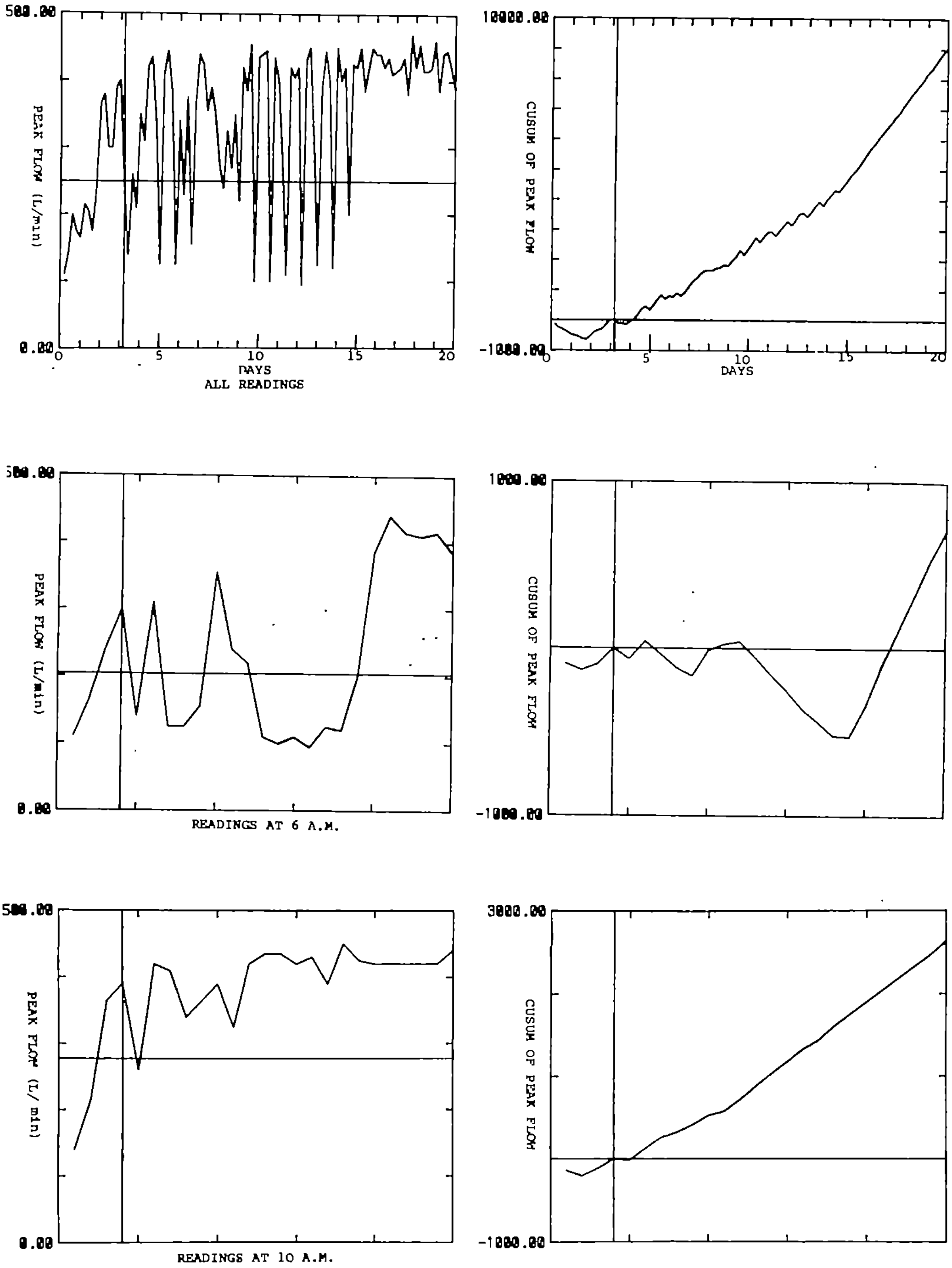

Fig. 3. Top, Serial PF readings taken throughout the day and derived cusum of an 'early morning dipper'. *Centre,* Serial PF readings at 6.00 a.m. only and derived cusum of the same patient. *Below,* Serial PF readings at 10 a.m. only and derived cusum of the same patient

Of the ten patients with acute asthma, nine had rapid improvement in their serial PF readings, mirrored by positive cusum slopes. Their PF and cusum charts resembled Fig. 1. The tenth patient showed little obvious change in PF readings, but did have a positive cusum slope (Fig. 2). She died unexpectedly following sudden deterioration with worsening airways obstruction on the seventh day. Taken alone the cusum analysis would have forecast an optimistic outcome which would clearly have been misplaced.

Of the ten patients with chronic asthma, four had improvement in PF readings, derived cusum slopes and symptoms (Fig. 3). One of these patients had pronounced morning dips. An interesting consequence of applying this technique is that it demonstrated the dissociation of PF readings at 6 a.m. (morning dips) from PF readings during the rest of the day, which is an objective illustration of a phenomenon previously described (Turner-Warwick 1977).

Two patients had deterioration in PF readings, cusum and symptoms (Fig. 4), and one patient had no change in PF readings, cusum or symptoms during intensive treatment. The remaining three patients had no obvious change in PF readings on visual inspection but did have positive cusum slopes. Fig. 5 is data from one of these patients who had 'brittle' asthma (Turner-Warwick 1977) and wide swings on the PF chart which show no obvious trend. Cusum analysis revealed improvement following introduction of bromocriptine (PF measurements were recorded as zero when the patient was so dyspnoeic that the PF was unrecordable).

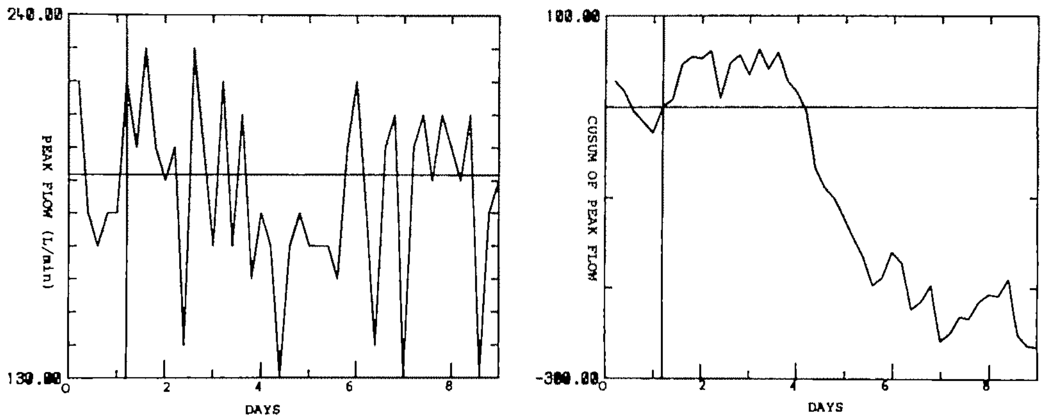

Fig. 4. PF readings and cusum of an asthmatic patient who deteriorated following a change in therapy. Cusum analysis indicated a deterioration not so apparent from the PF chart alone

We thought cusum analysis might be helpful in demonstrating minor degrees of change in serial measurement of PF. We applied this technique to seven normal subjects before and during respiratory tract infections where small changes in PF are sometimes observed, but here cusum failed to expose trends where there was no obvious change in PF measurements and simply paralleled changes where these were apparent in the serial PF readings.

Discussion

Cusum analysis is useful in detecting trends in serial measurements where the change of mean is small compared with the degree of scatter in the serial measurements. It is clearly superfluous where a trend is apparent from the serial measurements themselves. We found that the autoscale computer plot of the PF measurements often brought to light an apparent improvement or deterioration that was not visible on inspection of the bedside PF chart. It should be noted that in the management of asthma it is often impossible to obtain an adequate series of pretreatment PF readings upon which to base a cusum, since immediate treatment is required and this precludes the use of this technique in life threatening asthma.

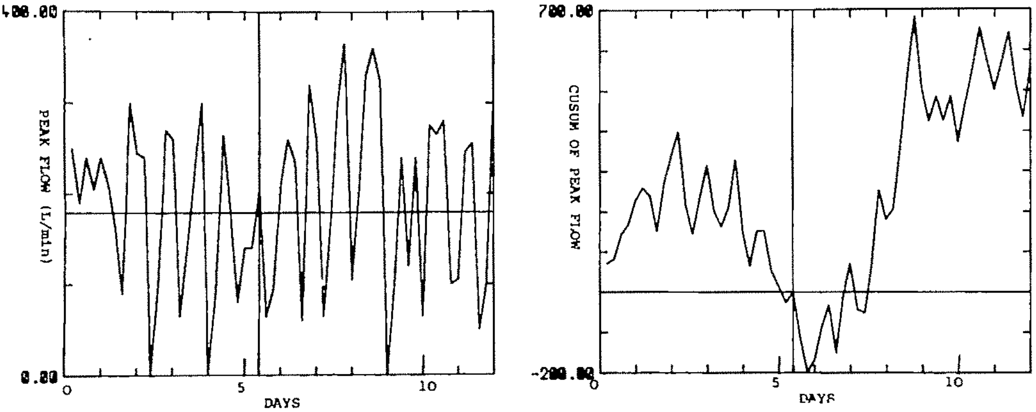

Fig. 5. PF Chart and cusum from a patient with brittle asthma, whose PF chart shows no obvious improvement despite bromocriptine treatment, whereas the derived cusum shows improvement.

There are some circumstances in which cusum analysis of serial PF measurements might be of practical value. First where there is wide scatter in the data and small therapeutic gains are considered clinically important (Fig. 5) (brittle asthma). Second where it is desirable to detect small changes, such as after adding another drug to an already complex drug regime, and third for early detection of improvement or deterioration during therapy, or of cessation of improvement during therapy. For example a trial of oral corticosteroids in chronic airways obstruction could be terminated early in the absence of response.

This study sought to assess the value of cusums for detection of changes in PF measurements. We conclude that cusum analysis is unlikely to become the basis of decision-making in asthma management, because in most cases, changes in peak flow patterns are obvious. The cusum analysis may reveal a trend when the PF chart shows no obvious change, but such change is unlikely to be regarded by the clinician as large enough to form the basis of a decision on treatment.

Appendix

Cusum calculation of a series $x_1, x_2, \ldots x_n$.
From each value a constant K is subtracted.
$K =$ the mean peak flow reading of the series prior to treatment.

Therefore $S1 = (x_1 - K)$

$S2 = (x_1 - K) + (x_2 - K) = S1 + (x_2 - K)$

$S3 = S1 + S2 + (x_3 - K)$

e.g. $K = 105$ litre/min

Pretreatment PF readings

95
120
90
125
120
80

Mean = 105

Subsequent PF readings	*Subtract K*	*Cusum*
95	−10	−10
100	−5	−15
80	−25	−40
120	+15	−25
140	+35	+10
135	+30	+40
90	−15	+25

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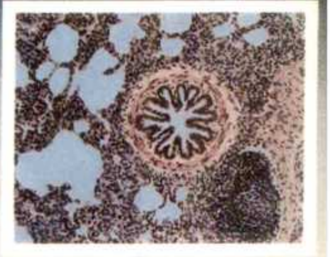

Cross-section of bronchiole illustrating bronchospasm due to contraction of respiratory smooth muscle.

“Why are so many asthma patients treated with oral drugs when their symptoms could be more effectively controlled, and with much less risk, by therapy administered by inhalation? ... All patients with asthma should be treated with a bronchodilator aerosol, and it is rational to use only the more selective sympathomimetic drugs...”

(*Modern Medicine*, May, 1977, p. 57-58)

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PATIENT INSTRUCTION

It is important to ensure that patients receiving inhalation therapy are correctly instructed in the use of the device being prescribed. For this purpose demonstration units are available on request from Allen & Hanburys Ltd. The patient's acquired technique should be monitored by re-checking at suitable intervals. Generally speaking, patients unable to use pressurised aerosols efficiently can be satisfactorily treated using the alternative Rotacap/Rotahaler system which, for them, provides a greater degree of certainty and a better guarantee of effectiveness. Any initial problems with the manipulation of the Rotahaler are usually overcome as the patient becomes more familiar with its use. In the case of young children and patients with arthritis of the hands it may be preferable for the device to be loaded by the parent or other person. When Ventolin Rotacaps are being used for the relief of acute bronchospasm it may be convenient to load a Rotacap into the device so that the dose is readily available. Ventolin and Becotide Rotahalers are supplied in plastic boxes for carrying in the pocket or handbag. The daily requirement of Rotacaps may be inserted into the spaces provided in the box to encourage compliance. A replacement Ventolin or Becotide Rotahaler should be prescribed at approximately six-monthly intervals.

RODUCT INFORMATION

ESENTATION AND BASIC NHS COST
ntolin Inhaler is a metered-dose aerosol delivering 100mcg salbutamol BP per actuation
ch canister contains 200 inhalations. Basic NHS cost £2.86
ntolin Rotacaps 200mcg & 400mcg each contain a mixture of the stated amount of
crofine salbutamol BP (as sulphate), and larger particle lactose in light blue/colourless or
k blue/colourless hard gelatine cartridges, respectively. Containers of 100. Basic NHS
t £4.41 and £5.96, respectively.
ntolin Rotahaler for use in conjunction with Ventolin Rotacaps. Basic NHS cost 65p.

ICATIONS
utine control of bronchospasm in bronchial asthma, bronchitis and emphysema, or as
uired to relieve attacks of acute bronchospasm. Doses may also be taken before exertion
revent exercise induced asthma or before exposure to a known unavoidable challenge.

SAGE AND ADMINISTRATION
single doses for the relief of acute bronchospasm, for managing intermittent episodes
sthma and to prevent exercise-induced bronchospasm.
ng Ventolin Inhaler – *Adults:* one or two inhalations.
ldren: one inhalation increasing to two if necessary.
ng Ventolin Rotahaler – *Adults:* one Ventolin Rotacap 200mcg or 400mcg.
ldren: one Ventolin Rotacap 200mcg.
chronic maintenance or prophylactic therapy.
ng Ventolin Inhaler – *Adults:* one or two inhalations three or four times a day.
ldren: one inhalation three or four times a day increasing to two inhalations if necessary.
ng Ventolin Rotahaler – *Adults:* one Ventolin Rotacap 400mcg three or four
es a day.
ldren: one Ventolin Rotacap 200mcg three or four times a day.
optimum results in most patients inhaled Ventolin should be administered regularly.

NTRA-INDICATIONS
ntolin preparations should not be used for the prevention of threatened abortion.

ECAUTIONS
previously effective dose of inhaled Ventolin fails to give relief lasting at least 3 hours,
patient should be advised to seek medical advice. Ventolin should be administered
tiously to patients suffering from thyrotoxicosis. Unnecessary administration of drugs
ing the first trimester of pregnancy is undesirable.

E EFFECTS
important side effects have been reported following treatment with inhaled Ventolin.

ODUCT LICENCE NUMBERS
ntolin Inhaler 0045/5022; Ventolin Rotacaps 200mcg 0045/0116;
ntolin Rotacaps 400mcg 0045/0117.

PRODUCT INFORMATION

PRESENTATION AND BASIC NHS COST
Becotide Inhaler is a metered-dose aerosol delivering 50mcg beclomethasone dipropion
BP per actuation. Each canister contains 200 inhalations. Basic NHS cost £4.34.
Becotide Rotacaps 100mcg & 200mcg each contain a mixture of the stated amount of microfine beclomethasone dipropionate BP and larger particle lactose in buff or chocola
brown/colourless hard gelatine cartridges, respectively. Containers of 100. Basic NHS co
£6.60 and £8.79, respectively.
Becotide Rotahaler, for use in conjunction with Becotide Rotacaps. Basic NHS cost 65p.

INDICATIONS
Bronchial asthma especially in patients whose asthma is not adequately controlled by bronchodilators and patients with severe asthma who would otherwise be dependent on systemic corticosteroids or adreno-corticotrophic hormone (ACTH) or its synthetic equivalent.

DOSAGE AND ADMINISTRATION
Using Becotide Inhaler – *Adults:* two inhalations three or four times a day is the usual maintenance dose. In severe cases dosage may be started at twelve to sixteen inhalations per day and subsequently reduced when the patient begins to respond.
Children: one or two inhalations, two, three or four times a day according to the response
Using Becotide Rotahaler – *Adults:* one 200mcg Becotide Rotacap three or four times a day is the usual maintenance dose.
Children: one 100mcg Becotide Rotacap, two, three or four times a day according to the response.
For optimum results inhaled Becotide should be administered regularly.

CONTRA-INDICATIONS
No specific contra-indications to inhaled Becotide are known but special care is necessar in patients with active or quiescent pulmonary tuberculosis.

PRECAUTIONS
The maximum daily intake of beclomethasone dipropionate BP should not exceed 1mg. Inadequate response after the first week of inhaled Becotide therapy suggests that excessive mucus is preventing penetration of inhaled drug to the target area. A short cour of systemic steroid in relatively high dosage should be given and therapy with inhaled Becotide continued.
Unnecessary administration of drugs during the first trimester of pregnancy is undesirab
When transferring patients to Becotide from systemic steroid therapy the possibility of adrenocortical suppression should be considered and patients given a supply of oral steroids for use during periods of stress. Please refer to the detailed procedure described the data sheets for Becotide Inhaler and Becotide Rotacaps.

SIDE EFFECTS
Occasional candidiasis of the mouth and throat (thrush) occurs in some patients, particularly those with high blood levels of Candida precipitins. Topical therapy with antifungal agents usually clears the condition without withdrawal of Becotide.

PRODUCT LICENCE NUMBERS
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Becotide Rotacaps 200mcg 0045/0120.

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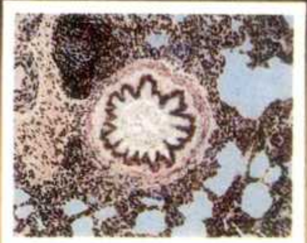
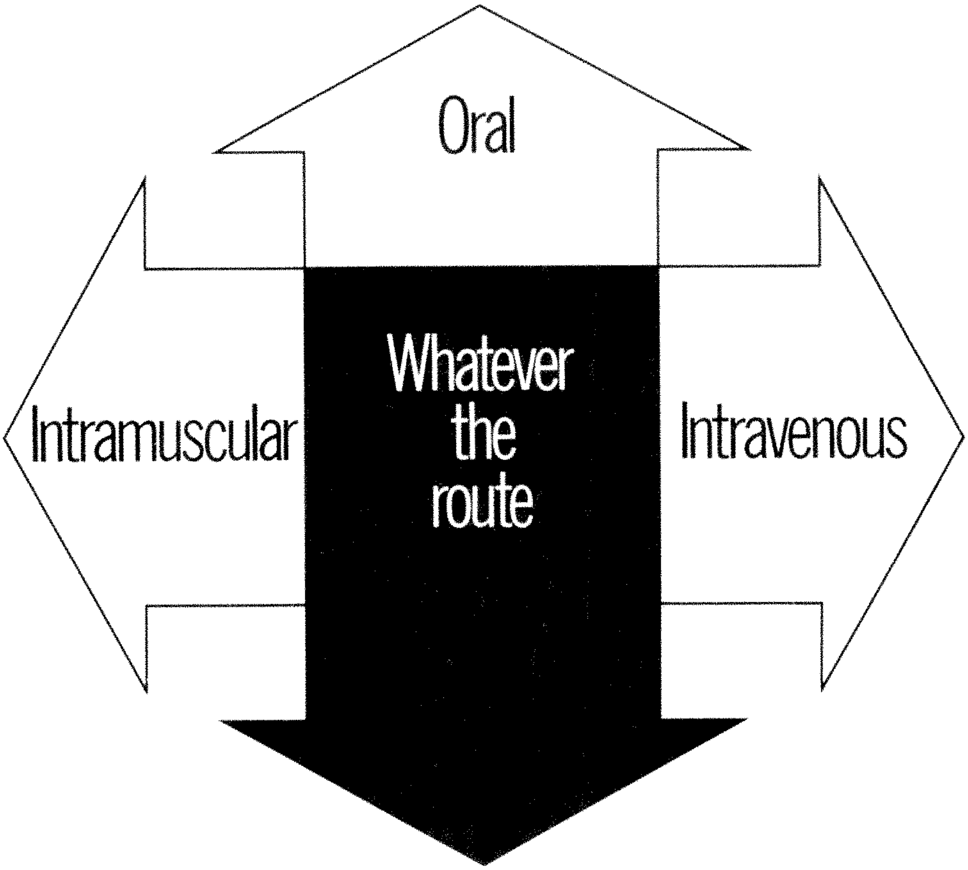


Cross-section of bronchiole illustrating bronchospasm complicated by bronchial mucosal oedema and hypersecretion of mucus.

"To support this claim of extraordinary activity (of Becotide), there are not only statistically valid comparisons but also numerous validated individual experiences. These include the impressive therapeutic results in patients with severe asthma not controllable with high daily doses of systemic steroids; the beneficial responses of those refractory to adrenergic agonists and unable to tolerate even suboptimal doses of theophylline; the suppression of asthma unresponsive to mediator-release inhibitors, such as cromolyn sodium; and, importantly, the high level of acceptance and compliance among people who do not comply with other standard therapeutic routines."

(*Lancet*, 1979, **i**, 932-933)



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Ref 1 Lancet 1976, **2**, 616

Indications
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Contra-indications and Precautions
Contra-indicated for patients with known hypersensitivity to cephalosporins.
Caution should be exercised in patients with known hypersensitivity to penicillins.
In all patients with reduced renal function, dosage should be suitably adjusted.
As with all drugs, caution should be exercised when used during pregnancy.
Prolonged use may result in overgrowth of non-susceptible organisms.
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Br. J. Dis. Chest (1980) *74*, 175

BECLOMETHASONE DIPROPIONATE IN ASTHMA: A COMPARISON OF TWO METHODS OF ADMINISTRATION

S. S. Chatterjee and A. G. Butler

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Summary

Beclomethasone dipropionate inhaled as a dry powder in doses of 200 μg four times a day was compared with the usual dose of 100 μg four times a day from a pressurized aerosol in 65 patients with asthma who used pressurized aerosols correctly. Each treatment was given for an eight-week period. The dry powder did not show any clinically significant advantage over the aerosol in terms of ventilatory function as measured by FEV_1 and the daily peak flow measurements during both treatments did not differ. The incidence of oral candidiasis was low and no other side-effects were encountered. It was concluded that beclomethasone dipropionate in dry powder form was as effective as aerosol in the treatment of asthma.

Introduction

The delivery of beclomethasone diproprionate by means of a pressurized aerosol has now gained widespread acceptance (Cameron et al. 1973; Cooper & Grant 1977). The degree of success in weaning patients from oral corticosteroids with beclomethasone dipropionate has varied between 20% and 90% (Brown et al. 1972; Maberly et al. 1973; British Thoracic and Tuberculosis Association 1976; Godfrey et al. 1978). This wide divergence might well be due to the severity of the disease, the differing criteria of the various protocols and the ability of patients to use a pressurized aerosol correctly. Many patients have good synchronization and their asthma symptoms are well controlled by beclomethasone dipropionate given from a pressurized aerosol (Lal et al. 1972).

It has been reported (Hartley et al. 1977) that salbutamol inhaled as a dry powder from a breath actuated device benefited those patients who were unable to coordinate the use of a pressurized aerosol. In order to compare the efficacy of the two routes of administration in patients who used aerosols correctly, we have carried out a four-month double-blind crossover trial to compare the efficacy of beclomethasone dipropionate inhaled as a dry powder with that from a pressurized aerosol in patients with satisfactory aerosol technique.

Patients and Methods

Seventy adult out-patients with asthma, from whom informed consent was obtained, were admitted to the trial. The results from 65 patients have been analysed. Five patients were excluded for the following reasons: one failed to return data; two defaulted for one month; one developed a diffuse rash and was withdrawn from the study; and one was withdrawn because of persistent thrush with both active treatments.

Forty-nine of the patients were male and 16 female. Their ages ranged from 20 to 79 years (median 48 years). All were regular users of beclomethasone dipropionate by aerosol and had been treated at a dose of 400 μg/day for a period of between two months and five and a half years with a median duration of three years. Every patient used salbutamol from a pressurized aerosol and 21 patients also took salbutamol tablets (2 mg) when required. Fifty-one of the 65 patients had good control of asthma symptoms while taking beclomethasone dipropionate and did not take oral corticosteroids, but 14 patients required oral prednisolone in addition to beclomethasone dipropionate aerosol and had in the past required higher daily doses of oral corticosteroids. On entry to this trial each patient was taking the lowest effective dose of oral prednisone (minimum 2 mg/day, maximum 7 mg/day), and total withdrawal of oral steroids had failed previously despite repeated attempts.

Before the study it was confirmed that the patients were able to use a pressurized aerosol and the dry powder inhaler. The trial was a double-blind comparison between (1) 200 μg beclomethasone dipropionate dry powder plus placebo aerosol and (2) 100 μg beclomethasone dipropionate from a pressurized aerosol plus placebo dry powder. Patients received each treatment for eight weeks in random sequence. Each treatment was taken four times daily, the powder always preceding the aerosol. The active powder contained 200 μg of microfine beclomethasone dipropionate mixed with lactose in a hard gelatine capsule (Becotide Rotacaps) and was inhaled from a Rotahaler, a device described by Hallworth (1977). The beclomethasone dipropionate aerosol was of conventional design. The placebo capsules contained only lactose whilst the placebo aerosol held only the inert propellant gases.

A short tetracosactrin stimulation test was carried out on each patient before the trial and was repeated after eight and 16 weeks, plasma cortisol levels being determined by the competitive protein binding assay method of Murphy (1967). A clinical assessment was made every four weeks when measurements of FEV_1 and FVC were made using a dry wedge spirometer (Vitalograph), having first determined that the patients had not used any form of bronchodilator therapy for the previous 12 hours. Mouth swabs for culture of *Candida* were taken and the buccal cavity was inspected, always by the same physician. Diary cards were completed by every patient on which they entered the number of times they used salbutamol each day and details of any other treatments taken, particularly oral corticosteroids. A mini Wright Peak Flow Meter was issued to each patient and peak expiratory flow rate (PEFR) was measured twice daily at 8 a.m. and 8 p.m., the best of three blows being recorded. Undesirable effects were detected by indirect questioning. Patient preferences and physician opinions were recorded at the end of the trial.

Results

Group I comprised 34 patients who used the active beclomethasone dipropionate powder during the first two months and the active aerosol during the second two months. The 31 patients in Group II received the active treatments in the reverse order. The mean values for the pulmonary function data at the end of each two months treatment period and pre-trial are shown in Table I.

Wilcoxon's rank sum test was used to detect significant treatment differences, sequence effects and period effects. Wilcoxon's signed rank test was used on readings for which no significant treatment effect existed to determine whether there had been a change from the initial level during the trial. As can be seen from Table I, the mean values of FEV_1 and FVC were similar at the end of both treatment periods. For the combined groups mean FEV_1 after 800 μg of active powder was 2.2 litres compared with 2.1 litres after 400 μg of beclomethasone dipropionate delivered by aerosol but because most individual patient values were greater after active powder treatment, the differences between the two routes of administration were statistically significant ($P < 0.001$). This was also true of the values for FVC. A statistically significant sequence effect was not detected.

The means of the morning and evening PEFR values recorded at home by the patients during the second month of treatment are shown in Table II. The application of Wilcoxon's rank sum test to these data did not reveal any statistically significant differences. The mean number of puffs of salbutamol taken by the 34 patients in Group I while using active powder was 169, and while using the active aerosol was 175. Patients in Group II were not as accurate in recording their salbutamol usage. Twenty-seven of the 31 recorded taking 198 puffs of salbutamol while using active aerosol while 24 of the 31 patients recorded a total of 223 puffs when using the active powder.

Table I. Mean values for FEV_1, FVC and $FEV_1/FVC\%$ before the trial and at two and four months

	FEV_1 (litres)	*FVC* (litres)	*FEV_1/FVC* (%)
Group I, powder first ($n = 34$)			
Pretrial	2.0	3.6	55
After powder at two months	2.3	3.6	62
After aerosol at four months	2.2	3.4	65
Group II, aerosol first ($n = 31$)			
Pretrial	1.8	3.4	52
After aerosol at two months	1.9	3.2	57
After powder at four months	2.1	3.5	60

Table II. Mean PEFR values recorded during the second month of of each treatment

	Group I ($n = 34$)	*Group II* ($n = 31$)	*Overall mean*	*P Value*
Powder (morning)	365	337	351	NS
Aerosol (morning)	369	313	341	
Powder (evening)	374	348	361	NS
Aerosol (evening)	381	328	355	

Patients in Group I reported taking 72 salbutamol tablets during eight weeks of treatment with active powder and 67 tablets while taking active aerosol.

When admitted to the trial 14 patients were still taking oral corticosteroids and this treatment was continued during the trial. One patient in Group I whilst on active powder needed a short course of oral corticosteroids for three weeks while one patient, also in Group I but using the active aerosol, also required a one-week course of oral corticosteroids.

There were some minor variations in the plasma cortisol levels between the different treatments in individual patients, but none of these indicated that the inhalation of beclomethasone dipropionate as a dry powder suppressed hypothalamic–pituitary–adrenal (HPA) axis function.

Four cases of oral candidiasis were noted (4.6%), three in the group who used the active powder first and one in the group who used the active aerosol first. All four cases responded to treatment with local amphotericin and beclomethasone dipropionate therapy was not discontinued or interrupted. No other side-effects were noted or elicited on direct questioning.

Analysis of patients' treatment preferences showed that 32 patients preferred the aerosol against 14 favouring the powder, with 16 patients having no preference. The physicians' opinions on the effect that treatment with the active powder had on the patients' asthma indicate that 41% were considered to have improved, 45% were unchanged and 10% deteriorated slightly.

Discussion

Our aim in carrying out this trial was to see whether beclomethasone dipropionate in powder form was as effective as the aerosol in controlling asthma in patients who apparently used aerosols correctly and efficiently. Some asthma patients have been deprived of effective use of steroid by inhalation because of their inability to use a pressurized aerosol efficiently. Earis and Bernstein (1978) reported that up to 25% of their patients were unable to coordinate finger pressure on the aerosol with inspiration, whilst the figure reported by Godfrey (1979) was as high as 50%. Paterson and Crompton (1976) showed that most people who cannot use a pressurized aerosol efficiently can use a powder inhaler which is triggered by the patient's own inspiratory effort. The Rotahaler is similar in that powder is delivered only during inspiration, but the two halves of the cut capsule liberate the powder into the airstream generated by the patient's inspiration. We noted that the majority of patients were able to empty the capsule with one inhalation.

We conclude that the Rotahaler is an effective method of administering beclomethasone dipropionate and is acceptable as far as the patient is concerned, although the majority stated a preference for the aerosol.

Acknowledgements

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PNEUMOTHORAX ASSOCIATED WITH PRIMARY BRONCHIAL CARCINOMA

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INTRODUCTION

Heimlich and Rubin (1955) reported three cases of primary bronchial neoplasm in which the presenting feature was a pneumothorax. Citron (1959) described a further six cases of bronchial neoplasms associated with pneumothoraces but since then there have been only sporadic reports of this unusual association.

We have seen four examples of pneumothoraces in patients with primary bronchial carcinoma during a six-month period. These are described as a reminder that carcinoma of the bronchus should be considered in older patients with pneumothoraces.

The presenting features, radiographic and histological findings in these four patients are summarized in Table I.

DISCUSSION

Pneumothorax and bronchial carcinoma are two relatively common clinical conditions which are occasionally found together. About 30 cases of pneumothorax associated with carcinoma of the bronchus have been described in the literature and in a review of 1143 cases of spontaneous pneumothorax seen at the Mayo Clinic over a 20 year period, Dines et al. (1973) found only four patients with a primary lung tumour. The association of pneumothorax with secondary lung tumours appears to be more common and there is a particular link with sarcomas. In the Mayo Clinic series, five patients had metastatic sarcomas and a review of 42 cases of pneumothorax with metastatic lung disease revealed 16 with osteogenic sarcoma (Janetos & Ochsner 1963). Many of the cases with metastatic disease have occurred in children. The histology of primary bronchial neoplasms was not always recorded in these reports but adenocarcinomas and alveolar cell carcinomas appear to be more common and oat-cell less common than would be expected from the overall proportions of different cell types. This may reflect the more peripheral site of alveolar cell carcinomas and adenocarcinomas increasing the likelihood of pleural involvement and the more central site and often small size of oat cell carcinomas (Spencer 1977).

A number of mechanisms have been postulated for the production of these pneumothoraces. In all reported cases the pneumothorax occurred on the same side as the tumour, making a chance association unlikely. Various diagnostic and therapeutic procedures such as biopsy, bronchoscopy and radiotherapy can produce pneumothoraces.

The most commonly suggested mechanism is direct invasion of the pleura. In these cases a pleural effusion usually occurs which is often bloodstained. Our fourth case is probably an example of this mechanism with direct invasion into the ribs. The first three

Table I. Summary of cases

Case	*Age* (years)	*Sex*	*Presentation*	*Chest radiograph*	*Histology*	*Comments*	*Site of neoplasm*
1	71	M	Anorexia Weight loss	Collapsed right lung at presentation Right pneumothorax developed during re-expansion	Small-cell Anaplastic	Necrotic tumour seen in right main bronchus at bronchoscopy	Right main bronchus
2	55	M	Weight loss Cough Dyspnoea	Left pneumothorax at presentation Partial collapse of left upper lobe	Poorly differentiated Squamous	No pleural involvement at pneumonectomy	Left main bronchus
3	62	M	Chest pain Dyspnoea	Left pneumothorax at presentation Wide mediastinum Narrow left main bronchus	Squamous	Treated by intercostal drainage and mediastinal radiotherapy	Trachea and left main bronchus
4	62	M	Haemoptysis Chest pain Weight loss	Right pneumothorax developed after presentation Tumour invading right first rib	Poorly differentiated Squamous	Histology from biopsy of first rib	Right upper lobe

cases appear to represent 'obstructive emphysema' with partial obstruction of a bronchus causing a rise in transpleural pressure with rupture of a subpleural bleb or emphysematous bulla.

At pneumonectomy in Case 2 the tumour was central and the lung showed emphysema but not visible site of pleural rupture. In the first case the right lung re-expanded spontaneously, probably due to sloughing of part of the intrabronchial tumour, but the lung had been collapsed for some time and traction on pleural adhesions at the time of re-expansion may have contributed to the development of the pneumothorax.

These four cases represent an unusual association of primary bronchial carcinoma with spontaneous pneumothorax. In two instances the pneumothorax was the presenting feature. The chest radiograph may be difficult to interpret initially in the presence of a pneumothorax and, although infrequent, the possibility of carcinoma should be remembered in the older patient with a pneumothorax.

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Requests for reprints to: Dr P. J. Rees, Clinical Science Laboratories, Guy's Hospital, London Bridge, London SE1 9RT.

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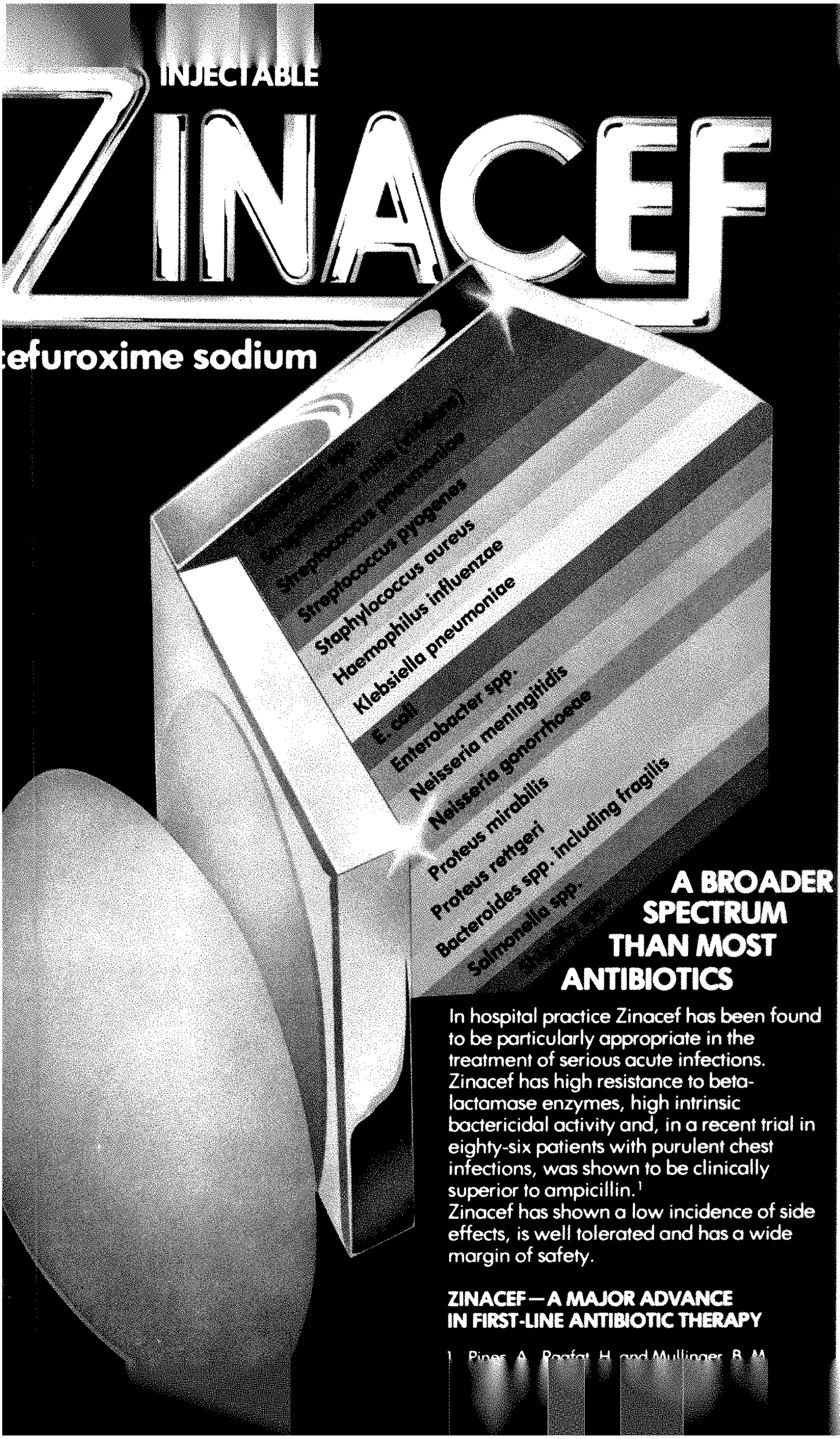

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TREATMENT OF ENDOBRONCHIAL AMYLOIDOSIS BY INTERMITTENT BRONCHOSCOPIC RESECTION

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Summary

In a patient with widespread endobronchial amyloidosis, the amyloid deposits resulted in severe disability over a ten-year period from obstruction of large airways and from recurrent chest infections and atelectasis. Repeated excision of small quantities of amyloid material during rigid bronchoscopy under general anaesthetic have resulted in symptomatic relief and measurable improvement of airways obstruction.

INTRODUCTION

Primary pulmonary amyloidosis is a rare cause of large airways obstruction. We report a case successfully treated by surgical excision and review the results of previously published cases treated in this way.

Case Report

A 49-year-old housewife presented with bronchitis during pregnancy in 1968 and again in 1969. During the latter year she developed streptococcal cellulitis of the right leg and a right lower lobe pneumonia which failed to resolve completely with antibiotics and physiotherapy. She was a non-smoker and gave a past history of hay fever. Prick skin tests were positive to mixed grasses and to milk.

In 1973 she was admitted to hospital in respiratory failure following a chest infection. She was severely dyspnoeic, cyanosed and wheezing. The chest radiograph showed basal consolidation, mainly on the right, and a small apical pneumothorax. The sputum contained pus with no eosinophils or pathogenic organisms. Blood gases on 24% oxygen were $P\text{O}_2$ 5.1 kPa (38 mmHg), $P\text{CO}_2$ 10.4 kPa (78 mmHg) and pH 7.28. Treatment was with IPP ventilation, antibiotics, bronchodilators, corticosteroids and bronchial lavage which produced frank pus. Following recovery, respiratory function tests demonstrated severe airways obstruction with an FEV_1 of 620 ml, FVC of 1200 ml, RV/TLC ratio of 70% and no response to inhaled salbutamol. A trial with 40 mg prednisolone daily resulted in a small improvement in airways obstruction and prednisolone was continued at 10 mg daily.

Subsequently she had recurrent severe chest infections with purulent sputum, leucocytosis and airway obstruction necessitating eight hospital admissions over a period of four years.

Fibreoptic bronchoscopy in 1976 revealed an irregular granularity of the mucosa of the large airways. Biopsy showed non-specific inflammatory changes, with no evidence of amyloid, even on later review with specific stains.

By 1978 the patient was obese, cushingoid and breathless on minimal exertion. There was loss of volume and diminished expansion of the right chest and dullness to percussion at the right base and widespread inspiratory and expiratory wheezing and coarse crepitations. General examination showed no evidence of amyloidosis affecting skin, gut, liver spleen or other organs.

Investigations included a normal full blood count, urea, electrolytes, creatinine clearance, and liver function tests, apart from a slightly elevated gammaglutamyl transpeptidase (31 IU/ml). The ESR was 14 mm/hour (Westergren). Plasma protein electrophoresis showed a slight increase in gammaglobulin but no monoclonal band. C_3 complement level was normal, but the C_4 level was elevated at 0.66 g/litre (normal 0.2–0.5 g/litre). The urine did not contain Bence-Jones protein. Serum α_1-antitrypsin was 5.39 g/litre (normal 2.0–4.0 g/litre). Serum precipitins to *Aspergillus fumigatus*, *Micropolyspora faeni* and budgerigar serum were not detected. The chest radiograph showed loss of volume of the right lung, pleural thickening, and nodular and linear shadowing at the right base (Fig. 1). Respiratory function tests showed severe fixed airways obstruction. FEV_1 was 850 ml, volume capacity 1620 ml with no improvement after inhalation of salbutamol. At bronchoscopy the larynx and trachea were normal but the carina was widened and grossly distorted (Fig. 2). The main and segmental bronchi were almost completely occluded by irregular yellow nodules.

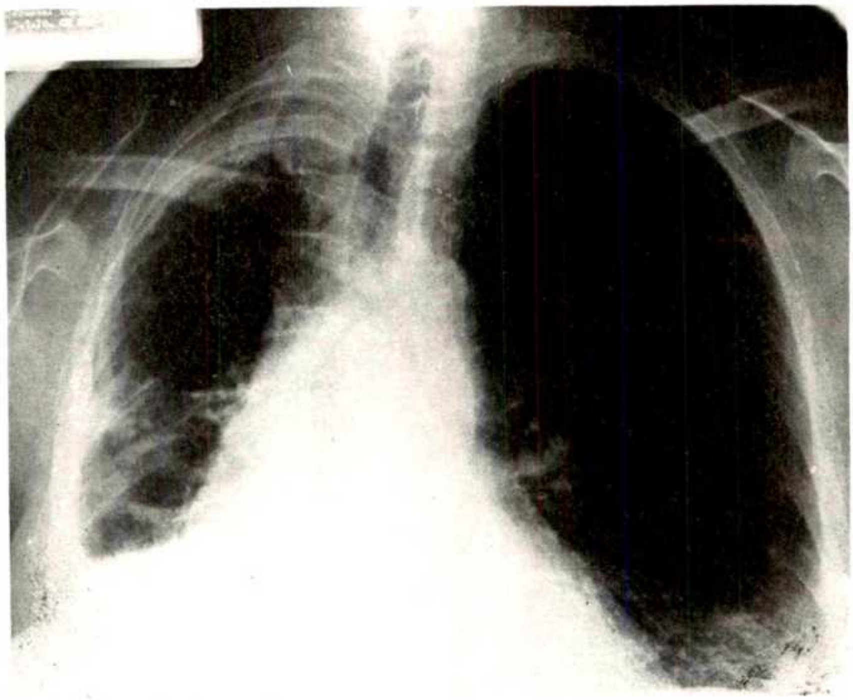

Fig. 1. Chest radiograph showing loss of volume on the right lung, pleural thickening and shadowing at the right base

Bronchial wall biopsy showed infiltration with plasma cells and eosinophilic material (Fig. 3) which stained for amyloid with Congo red, methyl violet and thioflavin. Amyloid fibrils were visible by electron microscopy and large areas of the bronchial mucosa were seen to lack cilial membranes. In other areas there was budding of new cilia. The internal cilial structure was normal. Gingival, rectal and trephine iliac crest marrow biopsies showed no evidence of amyloidosis.

Subsequent bronchoscopies performed by Mr J. C. R. Lincoln at regular intervals enabled small amounts of amyloid tissue to be removed from the main airways. Haemorrhage complicated the procedure twice and on both occasions stopped spontaneously. On one occasion the patient had to be maintained on IPPV for 24 hours. Initially the patient was breathless on minimal exertion such as dressing and was unable to perform standard exercise tests. After the fifth treatment she noticed symptomatic improvement. After the eleventh treatment she was able to walk up to one and a half miles and do her housework normally. Respiratory function tests demonstrate progressive deflation of the lungs with a fall in total lung capacity and residual volume (Fig. 4).

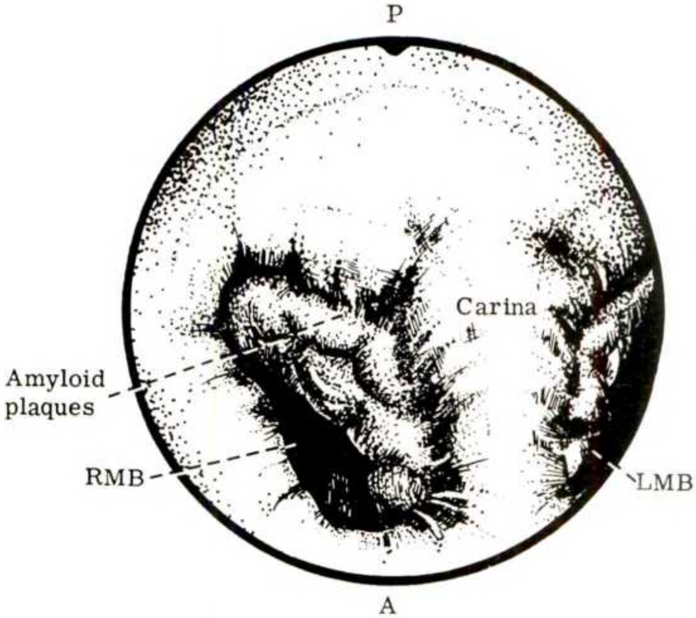

Fig. 2. Distorted carina and main bronchi line with amyloid deposits

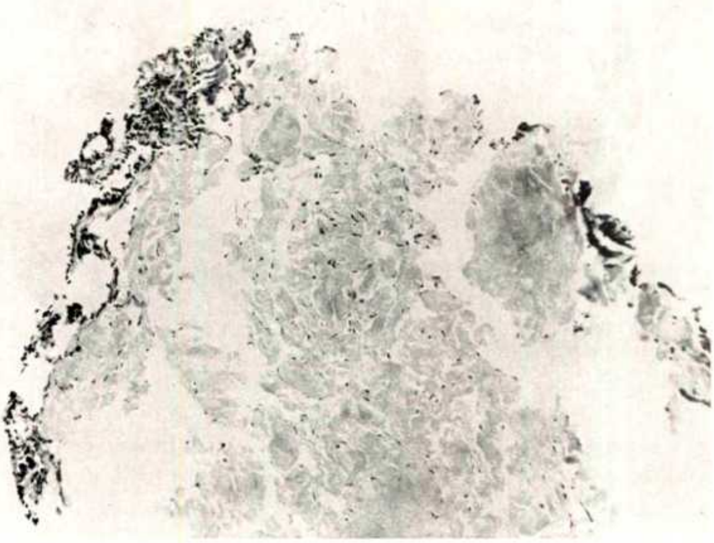

Fig. 3. Endobronchial polyp showing extensive deposition of amyloid beneath the basement membrane. H & E, low power

DISCUSSION

Amyloidosis is a rare condition which may be widespread throughout the body or confined to one organ. Primary pulmonary amyloidosis presents clinically either as a mass simulating tumour, as a diffuse reticulonodular pulmonary infiltrate, or as single or multiple nodular deposits in the tracheobronchial tree producing airways obstruction (Prowse 1958).

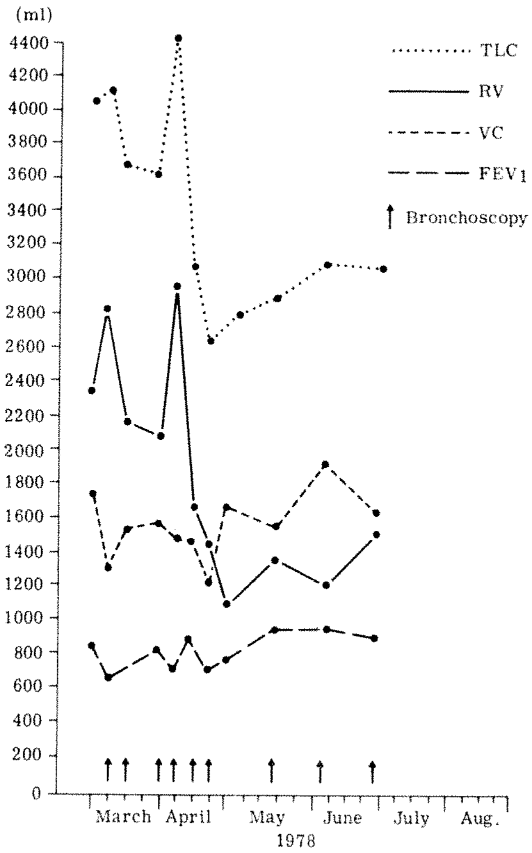

Fig. 4. Respiratory function tests during treatment, showing progressive deflation with relief of airway obstruction

Although tracheobronchial amyloidosis is rare a recent survey of the literature (Rubinow et al. 1978) revealed 41 cases to which the present case can be added. The presenting symptoms are cough, dyspnoea and wheezing which often as here lead to a mistaken diagnosis of asthma. Distal atelectasis is common with reduction of lung volume and secondary infection. The highly vascular friable lesions lead to haemoptysis. The disease is commoner in males than females, with an average age of 53 years on presentation. None of the reported cases have shown evidence of amyloid deposition outside the lower respiratory tract, despite post-mortem examination (Prowse 1958; Prowse & Elliott 1963; Jones & Chatterji 1977; Kanarek 1977; Rubinow et al. 1978).

Pneumonectomy (Weissmann et al. 1947) and radiotherapy (Shinoi et al. 1962) have been used to treat bronchopulmonary amyloidosis, but local bronchoscopic removal is the treatment usually recommended. Including the present case we found reports of 11 patients who had been treated with intermittent bronchoscopic resections, and all had been improved by this (Table I). At the time of reporting seven of these 11 patients survived having had an average of 5.4 resections over an average period of 20.6 months. Severe haemorrhage is a recognized complication of this procedure and caused death in three patients. Haemorrhage was not a problem in the remaining cases.

Table I. Results of intermittent bronchoscopic resection

Reference	*No. of resections*	*Survival* (months)	*Fate*
Rubinow et al. (1978)	Unspecified	72	Dead—bleeding
Prowse & Elliott (1963)	2	16	Dead—bleeding
Mainwaring et al (1969)	Unspecified	72	Dead—infection
Gottlieb & Gold (1972)	2	12→	Alive
Attwood et al. (1972)	13	72	Dead—bleeding
Schottenfeld et al. (1951)	13	12→	Alive
Domm et al. (1965)	3	6→	Alive
McGurk (1968)	3	24→	Alive
Holinger et al. (1950)	3	18→	Alive
Schmidt et al. (1953)	2	60→	Alive
Present case	12	25→	Alive

Our experience confirms the value of local resection of these lesions and suggests that satisfactory clearing of the large airways obstruction can be achieved safely, providing that small amounts of tissue are removed at frequent intervals.

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PULMONARY INFECTION CAUSED BY *MYCOBACTERIUM GORDONAE*

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Summary

Mycobacterium gordonae, a scotochromogenic organism, is considered a saprophyte. In sputum cultures the isolation of this organism or other species belonging to the scotochromogen group is not generally considered clinically significant since they are known to appear as commensals. We report the case of a 50-year-old man with pulmonary infection caused by *M. gordonae*. The clinical and radiographic findings in this case and the course are outlined. Diagnostic criteria of atypical mycobacterial infections are discussed and previously reported scotochromogenic infections briefly reviewed.

INTRODUCTION

The genus *Mycobacterium* is divisible into about 30 species, most of which are well defined. On the basis of their rate of growth and pigment production in light and in dark they may be placed in four groups, namely photochromogens, scotochromongens, non-chromogens and rapid growers (Runyon 1959). Although obsolete as a classification, this grouping permits a preliminary division of strains before more rigorous tests of identity.

The slow-growing scotochromogens include *Mycobacterium marianum* (*scrofulaceum*) *M. szulgai*, *M. xenopi*, *M. gordonae* and pigmented variants of *M. avium*. It is probable that *M. gordonae* is synonymous with *M. aquae* but this cannot be established for certain as the type strain of the latter species has been lost. With the exception of *M. gordonae*, the above scotochromogens, although primarily saprophytes, have been repeatedly implicated as pathogens (Lincoln & Gilbert 1972; Wolinsky & Jenkins 1974; Davidson 1976). A possible case of pulmonary disease due to *M. gordonae* was reported by Gracey and Byrd (1970) who described the responsible organisms as 'falling between the sub-groups of *M. scrofulaceum* and *M. aquae*'. Apart from this somewhat doubtful example, *M. gordonae* has never previously been implicated as a pathogen. In this paper we describe a case of pulmonary infection caused by this species.

Case Report

A 50-year-old man was admitted to hospital because of weight loss, night sweats, cough and haemoptysis. He had had pulmonary tuberculosis 20 years ago and had been treated with streptomycin, *para*-aminosalicyclic acid and isonicotinic acid for 18 months followed by left upper lobe lobectomy. There was no occupational history of organic dust exposure.

Five years ago the patient was assessed at another hospital for 'acute bronchitis', where it was noted that *M. kansasii* was isolated in one sputum culture, while several other mycobacterial cultures of the sputum were negative. This single isolation of *M. kansasii* was considered a commensal and no treatment was administered. Later in the same year he underwent bronchoscopy and bronchogram because of haemoptysis. There was no evidence of tumour or bronchiectasis and cultures of sputum and bronchial aspirates were negative for mycobacteria. Clinically and radiographically he remained stable on annual follow-up examinations. The chest radiograph one year before the present admission showed residual fibrotic and calcified densities which were unchanged from previous radiographs.

On admission he was afebrile and dullness to percussion and bronchial breath sounds on auscultation were noted over the left upper chest. The total leucocyte count was 8500/mm^3 with 67% segmented forms and 19% lymphocytes. Chest radiograph (Fig. 1) showed cavitation and pericavitary and dense apical infiltrates in the left upper lung field which were not present a year before. Nine consecutive cultures of sputum grew scotochromogenic mycobacteria which were niacin-negative and catalase-positive. Further differentiation was made by biochemical tests. Positive Tween 80 hydrolysis in five days and negative urease tests indicated that the species was *M. gordonae* rather than *M. scrofulaceum*. Negative nitrate reduction, aryl sulphatase reaction and resistance to INH, even at a concentration of 5 μg/ml, differentiated the organism from *M. szulgai*. The organisms were resistant to streptomycin, *para*-aminosalicylic acid, ethambutol and isoniazid and were partially sensitive to rifampin on indirect drug susceptibility tests.

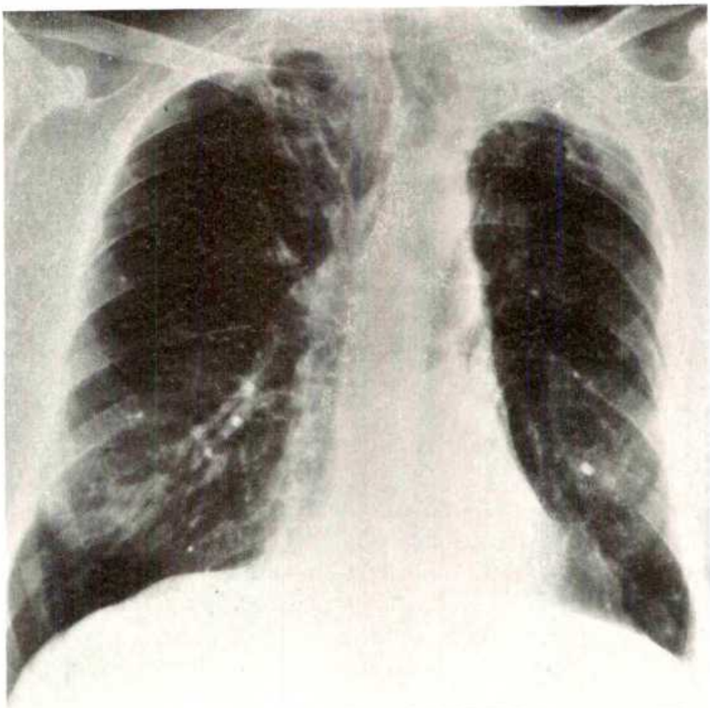

Fig. 1. Chest radiograph showing cavitation, pericavitary infiltrates and dense apical infiltrates

At fibreoptic bronchoscopy the left upper lobe stump was seen not to show any endobronchial lesion. Bronchial aspirate did not reveal malignant cells. No other mycobacteria or fungi were grown from the cultures. The patient was treated with rifampicin (600 mg/day) and ethambutol (1200 mg/day). The haemoptysis resolved spontaneously. After six months of treatment the sputum culture was still positive for *M. gordonae*. After one year, sputum cultures became negative and the cavitary and infiltrative chest radiograph findings improved. Treatment was discontinued after 22 months and the patient was followed as an out-patient for over four years. During this follow-up period he remained clinically and radiographically stable. Sputum cultures remained negative for mycobacteria.

DISCUSSION

The diagnosis of atypical mycobacterial infection is not free from difficulties, particularly when mycobacterial species normally considered saprophytic are encountered in the sputum of patients with lungs already damaged by tuberculosis or chronic obstructive lung disease. Yamamoto et al. (1967) and Jenkins (1959) outlined criteria to help differentiate between cases in which the isolated mycobacteria are probably saprophytes and those which are pathogens. Yamamoto et al. proposed that the diagnosis of atypical mycobacterial disease can be made in the presence of one of the following major criteria: (1) repeated discharge (more than four times) of atypical mycobacteria in large numbers (more than 10 colonies) and the presence of clinical symptoms which may be attributed to these bacilli; (2) the presence of a lesion containing atypical mycobacteria and histopathologic changes possibly due to these bacilli. The guidelines suggested by Jenkins are: (1) isolation of the organisms in the absence of other mycobacteria; (2) repeated isolation of the same organisms; (3) demonstration of mycobacteria by culture of resected material; (4) stronger cutaneous reaction to homologous PPD compared to standard PPD and the demonstration by agar gel diffusion techniques of specific antibodies in the serum; and (5) correlation of the isolate with clinical features. The findings in our patient agree with the diagnostic criteria of Yamamoto and Jenkins except that no comparative skin tests or gel diffusion tests were done and no surgical resection performed.

The clinical features and course of *M. gordonae* pulmonary infections are unknown. The case reported by Gracey and Byrd (1970), where the organism was not clearly differentiated but may have been *M. gordonae,* was that of a 48-year-old carpenter. The patient presented with a right upper lobe infiltrate and cavity. He had persistent cough and weight loss (25 lb in one year) and gave no past history of tuberculosis. After treatment for three months with isoniazid, *para*-aminosalicylic acid, streptomycin, cycloserine and ethionamide, acid-fast bacilli were still present in the sputum, but cultures were negative. Because of persistent acid-fast bacilli in the sputum and lack of response on the chest radiograph a right upper lobectomy was carried out. Although mycobacteria were seen on tissue stains, cultures of lung tissue did not yield mycobacteria. The patient reportedly remained well, but details of follow-up information are unknown.

In general, scotochromogenic pulmonary infections tend to affect people with pneumoconiosis (Wolinsky 1963). The clinical symptoms of scotochromogenic infections seemed milder, chest radiograph findings more limited, and the response to treatment better in scotochromogenic than in non-scotochromogenic pulmonary disease (Yamamoto et al. 1967).

ADDENDUM

Since the above report was submitted a case of systemic infection with *M. gordonae* that included infection of an aortic valve prosthesis has been reported (Lohr et al. 1978).

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CYSTIC THYMOMA SIMULATING PULMONARY STENOSIS

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Summary

A 36-year-old man presented with chest pain, an anterior mediastinal mass and a loud pulmonary systolic murmur. At operation a large, tense, well encapsulated, cystic thymoma was found to be compressing the right ventricular outflow tract and the main pulmonary trunk, producing a systolic thrill over the artery. After excision of the cyst, the thrill and the murmur disappeared and there was complete symptomatic relief. Classification, pathology, clinical presentation, diagnosis and treatment of cysts of the thymus are discussed. The syndrome of pulmonary artery compression characterized by a triad of chest pain, dyspnoea and a loud pulmonary systolic murmur, which decreases in intensity during inspiration, is described. Pertinent literature on cysts of the thymus, and acquired pulmonary stenosis due to extrinsic compression is reviewed.

INTRODUCTION

Acquired pulmonary stenosis from extrinsic compression of the right ventricular outflow tract and the main pulmonary artery by mediastinal tumours and cysts is an uncommon but a well documented condition (Babcock et al. 1962; Shaver et al. 1965; Gough et al. 1967; Seymour et al. 1968, Littler et al. 1970). Benign cystic thymoma as a cause of pulmonary artery compression has not been described before. The purpose of this paper is to report such a case and to review briefly the subject of cysts of the thymus and the syndrome of pulmonary artery compression.

Case Report

A 36-year-old man was admitted in September 1977 with an eight-month history of dull, central chest pain, with no radiation and unrelated to exercise. He gave no history of other chest symptoms, of rheumatic fever or family history of heart disease. The patient had been investigated for haemoptysis in 1969, but no cause for this had been found. Physical examination and a posteroanterior chest radiograph at that time were normal.

On physical examination he was a healthy looking man, with agenesis of his left ear. He was afebrile, had a pulse rate of 80/minute with normal peripheral pulses, and a blood pressure of 130/80 mmHg in both arms. There was no lymphadenopathy, hepatomegaly or splenomegaly. There was an area of dullness superiorly on the front of the left chest. Breath sounds were normal.

The apex beat was not displaced, there were no precordial thrills and the first and the second heart sounds were audible in all areas. The pulmonary second sound was widely split with little respiratory variation. A grade 3/6 ejection systolic murmur was audible over the left second intercostal space, radiating towards the left infraclavicular region. There was no change in the intensity of the murmur during inspiration or expiration. No ejection click was present and no diastolic murmurs were heard.

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On admission, the haematocrit, the liver function tests and the rest of the blood chemistry were normal. Wasserman's reaction, VDRL and TPHA were all negative. The electrocardiogram showed sinus rhythm with a normal axis. Chest radiograph showed normal lung fields, normal cardiac contour, and a large, well defined, anterior, superior mediastinal mass.

A diagnosis of thymic tumour was made and surgical exploration was felt to be indicated. The approach was through a median sternotomy and, on retraction of the sternal edges, a tense, well encapsulated cyst, about 10 cm in diameter and with evidence of haemorrhage into the lumen was found in the anterior mediastinum. The pericardium was opened and the intrapericardial structures were found to be markedly displaced posteriorly. A systolic thrill was palpable over the pulmonary artery. The cyst was dissected out easily and excised. The thrill over the pulmonary artery disappeared after removal of the cyst.

Post-operative progress was uneventful. The pulmonary systolic murmur disappeared and he was discharged on the eleventh post-operative day. Six months later he was symptom-free and a chest radiograph was satisfactory.

Pathology

The collapsed unilocular cyst was about 10 cm in diameter and weighed 113 g. The outer surface was fairly well circumscribed and encapsulated but the inner surface of the cyst looked fleshy and had small lobulated projections into the cavity.

The wall of the cyst was composed of a large number of mature lymphocytes and a lesser number of ovoid epithelial cells. These cells had pale cytoplasm with indistinct cell membranes and round, oval, vesicular nuclei. No mitotic figures were seen. There were large numbers of phagocytic histiocytes, especially towards the periphery of the cyst wall, giving it a 'starry-sky' appearance. Another morphological feature was a collection of eosinophilic fluid around small vessels, giving an appearance of fluid-filled microcysts. Careful search did not show any Hassall's corpuscles. A diagnosis of cystic thymoma was made and it was considered to be benign on gross and morphological features.

DISCUSSION

The nature of mediastinal thymic cysts is still controversial and many classifications have been put forward (Speer 1938; Krech et al. 1954; Bieger & McAdams 1966; Mikal 1974). The most functional and widely accepted classification was proposed by Krech et al. (1954) who divided thymic cysts into three groups; inflammatory, congenital and neoplastic. However, this simple classification ignored the lymphatic cysts and cystic lymphangiomas which may occur in the thymus, and cystic teratoma (dermoid cyst), which is also included in some definitions of thymic cysts (Dyer 1967).

During the nineteenth century, virtually all cysts of thymic origin were found at necropsy in infants suffering from congenital syphilis. These 'Dubois' abscesses' were regarded as syphilitic by most authors, although there was some argument about the part played by tuberculosis in their development (Krech et al. 1954).

Loupalt in 1897 recorded the first congenital thymic cyst, a necropsy finding in an 18-year-old girl (Podolsky et al. 1962). Congenital cysts may occur anywhere along the line of embryologic descent extending from the angle of the mandible into the anterior mediastinum. These cysts are generally believed to be due to fluid or haemorrhagic distension of persistent tubular remnants of the third pharyngeal pouch.

Pathologically, the congenital cysts can vary greatly in size, may be unilocular or multilocular and usually contain a chocolate-coloured fluid composed of old blood and cellular debris. The lining of the cysts may be flattened, cuboidal, columnar, ciliated columnar or squamous epithelium. Cholesterol crystals may be embedded in the wall forming cholesterol clefts and cholesterol granulomas and occasionally haemorrhage into the cyst wall is also seen. The epithelial lining of the cyst wall may be destroyed by infection or pressure necrosis so that only a fibrous shell remains. The presence of normal thymic tissue within or adjacent to the cyst wall is essential for the diagnosis (Dyer 1967; Allee et al. 1973; Mikal 1974).

Thymoma is the most frequently encountered anterior mediastinal neoplasm (Bernatz et al. 1961). Visible cyst formation is a characteristic feature of this tumour and is seen in 40% of the neoplasms (Rosai & Levine 1976). The cystic spaces are most commonly considered to be the result of liquefactive necrosis or fluid accumulation secondary to haemorrhage. The size may vary from inconspicuous spaces to large cavities containing serous, putty-like grumous brown or haemorrhagic material, as was seen in our case. One of the most interesting histological features of thymoma is the formation of perivascular spaces. They are present in over half the tumours. The size varies from a tiny cleft to a cystic formation reaching a diameter of 1 mm or more (Rosai & Levine 1976). It has been stated that these spaces occur as a result of degeneration rather than secretory activity of the cells or proliferation and distension of lymphatic vessels, as had been suggested by some early workers (O'Gara et al. 1958). There were a large number of perivascular fluid filled microcysts in our case. It is proposed that one or more of these spaces distend as a result of fluid accumulation and may ultimately become large.

Some cysts of the anterior mediastinum defy diagnosis even after histological studies and these are usually classified as 'non-specific'. It is likely that the majority of the 'non-specific' mediastinal cysts filled with blood and cholesterol clefts are of thymic origin (Dyer 1967; Rosai & Levine 1976).

Shin and Levowitz (1973) on reviewing the literature found 58 reported cases of congenital thymic cysts, 40 of which were mediastinal, 14 cervical and four cervico mediastinal; 50% of these cases were in patients less than 20 years of age, with a male to female ratio of 3:2.

The patient with a thymic cyst may be symptom-free and a routine chest radiograph may reveal a mass in the anterior mediastinum. When symptoms do occur, they are probably related to haemorrhage into the cyst leading to increase in size and hence pressure on adjacent structures. The most frequent symptoms are pain or fullness in the chest and dyspnoea, which may be more severe when the patient is supine. Other less frequent symptoms are dysphagia, choking, non-productive cough, weight loss and tachypnoea. Thymic cysts may also present with acute cardiorespiratory distress (Greipp et al. 1973), Horner's syndrome (Sarma 1974), vocal cord paralysis (Bailey et al. 1977), loculated pneumomediastinum (Raila & McKerchar 1977) or may simulate cardiomegaly with haemodynamic abnormalities (Schluger et al. 1968; Hoose et al. 1971; Sauer et al. 1971). Cystic thymoma has been known to simulate constrictive pericarditis, with the intracardiac pressures returning to normal after removal of the cystic mass (Schloss et al. 1975). Cystic change in thymoma has no effect on the development of associated clinical syndromes like myasthenia gravis, hypogammaglobulinaemia, myocarditis, myositis, hyperglobulinaemic purpura, Sjögren's syndrome, Raynaud's phenomenon, anaemia and pancytopenia (Dyer 1967).

Anterior mediastinal tumours and cysts can mimic pulmonary stenosis, due to external compression. Littler et al. (1970) found 32 cases of pulmonary stenosis due to extrinsic compression reported in the literature. Since then, five more cases of acquired stenosis of the pulmonary artery caused by Hodgkin's disease (Vieweg et al. 1976), metastatic hypernephroma (Gordon et al. 1973), mediastinal fibrosis (Cosio et al. 1973), bronchogenic cyst (Harris et al. 1973) and aortic aneurysm (Saad et al. 1970) have been described. Tumours of the thymus with microscopic appearance of Hodgkin's disease (Winter 1958; Shaver et al. 1965), malignant thymoma (Littler et al. 1970) and congenital thymic cyst (Allee et al. 1973) have all been recorded as causing pulmonary stenosis. A large, benign cystic thymoma causing compression of the right ventricular outflow tract and the main pulmonary artery has not been reported before.

The rarity with which the pulmonary artery is compressed by a mediastinal mass is probably related to the fact that mediastinal tumours, in general, enlarge laterally. They are therefore more likely to produce superior vena cava obstruction than compression of the heart and the great vessels.

The syndrome of pulmonary artery compression is characterized by a triad of chest pain, dyspnoea and a loud pulmonary systolic murmur (Seymour et al. 1968). The two main features of our patient were chest pain and a loud systolic murmur and he admitted to minimal exertional dyspnoea only on direct questioning. Another useful sign is a decrease in the intensity of the systolic murmur during inspiration, which is attributed to the tumour being lifted off the pulmonary artery during inspiration (Littler et al. 1970). This, in fact, was absent in our patient.

All benign tumours and cysts of the mediastinum should be excised because of the very real possibility of pressure on adjacent vital structures, haemorrhage, rupture, infection or malignant change (Oldham 1971). As the histological diagnosis of thymic cysts and cystic thymomas can often only be made after surgical resection, it was decided not to carry out any further investigations before proceeding with surgery in our patient. The recommended surgical approach is through a median sternotomy, splitting the sternum over its full length. The incision may sometimes have to be extended into the neck, if the mediastinal cyst also has a cervical component. This approach allows complete exposure of the anterior mediastinum, and hence is recommended for surgical excision in all cases.

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PLEUROPULMONARY INFECTION DUE TO *CORYNEBACTERIUM STRIATUM*

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Summary

Corynebacterium striatum, a saprophytic diphtheroid in man, caused a pleuropulmonary infection in a patient with chronic lymphocytic leukaemia. This organism has not previously been described as a cause of human disease.

INTRODUCTION

The Corynebacteria are a group of aerobic, Gram-positive, non-sporulating, predominantly non-motile rods. Members of this genus other than *C. diphtheriae* are termed diphtheroids. Due to their saprophytic nature most diphtheroid isolates in man are ignored and attributed to contamination from skin or mucous membrane sources. We report a case of pleuropulmonary infection due to the diphtheroid *Corynebacterium striatum* in a patient with chronic lymphocytic leukaemia.

Case Report

A 79-year-old man was admitted to Wadsworth V.A. Hospital in March 1976 with a three-week history of anorexia, fatigue and shortness of breath. He had untreated chronic lymphocytic leukaemia, first diagnosed in 1954. Physical examination revealed a temperature of 40°C, a pulse rate of 110/minute, a respiratory rate of 36/minute and a blood pressure of 80/60 mmHg. Rales were present in the right lower lung field. There was neither lymphadenopathy nor hepatosplenomegaly.

Laboratory data included a haematocrit of 40% and a white blood cell count of 95 000 /mm^3 with 83% lymphocytes, 14% segmented neutrophils and 3% band forms. The platelet count was 64 000/mm^3. Arterial blood gases breathing room air were $P\text{O}_2$ 43 mmHg, $P\text{CO}_2$ 33 mmHg and pH 7.33. Bilateral interstitial and alveolar infiltrates were observed on the chest radiograph. The electrocardiogram showed sinus tachycardia and non-specific ST changes. Sputum cultures revealed *Haemophilus influenzae* and *Staphylococcus aureus*.

The patient was given intravenous fluids and ampicillin, oxacillin and gentamicin. Endotracheal intubation with mechanical ventilation was initiated. A normal tracheobronchial tree was noted on fibreoptic bronchoscopy. Bronchial washings were negative for acid-fast bacilli, fungi and *Pneumocystis carinii*. Tracheostomy and open lung biopsy were performed and revealed changes compatible with an acute interstitial pneumonia. Special stains and cultures were negative for *Pneumocystis carinii*, viruses, bacteria, fungi and acid-fast bacilli. The patient became afebrile and partial clearing of the radiographic infiltrates was noted. All antibiotics were discontinued. The patient continued to require mechanical ventilatory support. By April serial tracheal aspirates showed increasing numbers of Gram-positive rods and cultures revealed *Klebsiella pneumoniae* and a diphtheroid. Repeated chest radiographs showed the gradual progression of a new left-sided pulmonary infiltrate and pleural effusion. Two blood cultures and a culture of pleural fluid showed a Gram-positive rod, again characterized as a diptheroid. The blood isolate was sent to the Center for Disease Control, Atlanta, Georgia, and identified as *Corynebacterium striatum*. Carbenicillin administration was started on 4 May 1976 but intractable endotracheal bleeding and ventricular arrhythmia terminated in death on 10 May.

Autopsy examination confirmed the diagnosis of chronic lymphocytic leukaemia with splenomegaly and leukaemic infiltration of the kidneys, liver and bone marrow. Examination of the respiratory system revealed necrosis of the right half of the trachea from the tracheostomy stoma to the origin of the right subclavian artery. Cut surface of the lung revealed diffuse consolidation of the lung parenchyma involving all lobes. Microscopic examination showed organizing interstitial pneumonia, moderate lymphocytic infiltration and focal areas of necrosis and haemorrhage. Giant cells with intranuclear inclusion bodies were noted in the alveolar spaces. Post-mortem lung tissue culture was positive for cytomegalovirus. Diphtheroids were not identified. Post-mortem blood culture also was negative for diphtheroids.

Microbiology. The diphtheroid isolated from blood culture was sent to the Center for Disease Control, Atlanta, Georgia, for identification. The short Gram-variable rod was non-haemolytic on rabbit blood agar. No growth was obtained at 5°C. The organism grew best at 35–40°C. No motility was noted and spore stains were negative. The organism was catalase- and nitrate-positive. Esculin hydrolysis and urease production were negative. No growth was obtained on MacConkey's agar and the indole test was negative. Hydrogen sulphide was produced using the paper method but not on triple sugar iron slants. Growth on carbohydrate media provided acid reactions on glucose and sucrose. No change was observed on xylose, mannitol, lactose, and maltose media. No pigment was produced. The organism resembled *Corynebacterium striatum* (ATCC 6940, NCTC 764).

Antibiotic disc susceptibilities, performed by our laboratory for each of three tracheal aspirates, three blood cultures and one pleural fluid culture, were uniform. The organism was resistant to erythromycin, chloramphenicol, clindamycin, gentamicin and amikacin. Susceptibility to penicillin G, ampicillin, carbenicillin, cephalothin, tetracycline and vancomycin was demonstrated. Methicillin susceptibility was variable.

Early reports on *C. striatum* described the organism as a thick diphtheroid with clear-cut bars (hence *striatum*) and large irregular granules (Buchanan & Gibbons 1974; Eberson 1918). Recent work with this organism reveals it to be a normal inhabitant of the anterior nares and skin, especially in the face and upper torso where sebum content is high (Somerville 1973).

DISCUSSION

Diphtheroids known previously as saprophytes are now known to be associated with serious human infections which include endocarditis, osteomyelitis, meningitis, bacteraemia, adenitis, wound infection, hepatitis, pneumonia and lung abscess (Johnson & Kaye 1970; Kaplan & Weinstein 1969). *C. pyogenes* and *C. equi*, pathogenic diphtheroids in animals, have been reported also as causes of pleuropulmonary infection in man (Carpenter & Blom 1976; Chlosta et al. 1970; Gardner et al. 1976; Golub et al. 1967). The immunosuppressed or debilitated state is most often implicated as the antecedent condition. A history of animal contact is obtained in some patients.

Illness due to chronic lymphocytic leukaemia probably contributed to the development of *C. striatum* infection. The finding of cytomegalovirus in the lungs at autopsy attests to the debilitated state of our patient. Diphtheroids were first isolated after tracheostomy and the latter may have provided the portal of entry for *C. striatum*, since this organism is frequently isolated from the skin of the forehead, cheek, shoulder and back. Post-mortem lung tissue and blood cultures were negative for diphtheroids, suggesting that carbenicillin was an effective antimicrobial. Despite the usual susceptibility of diphtheroids to the pencillins and cephalosporins, consistent susceptibility to these antimicrobials is not demonstrated in some diphtheroid isolates (Hande et al. 1976). Complete antibiotic susceptibility studies are therefore mandatory in the treatment of diphtheroid infections.

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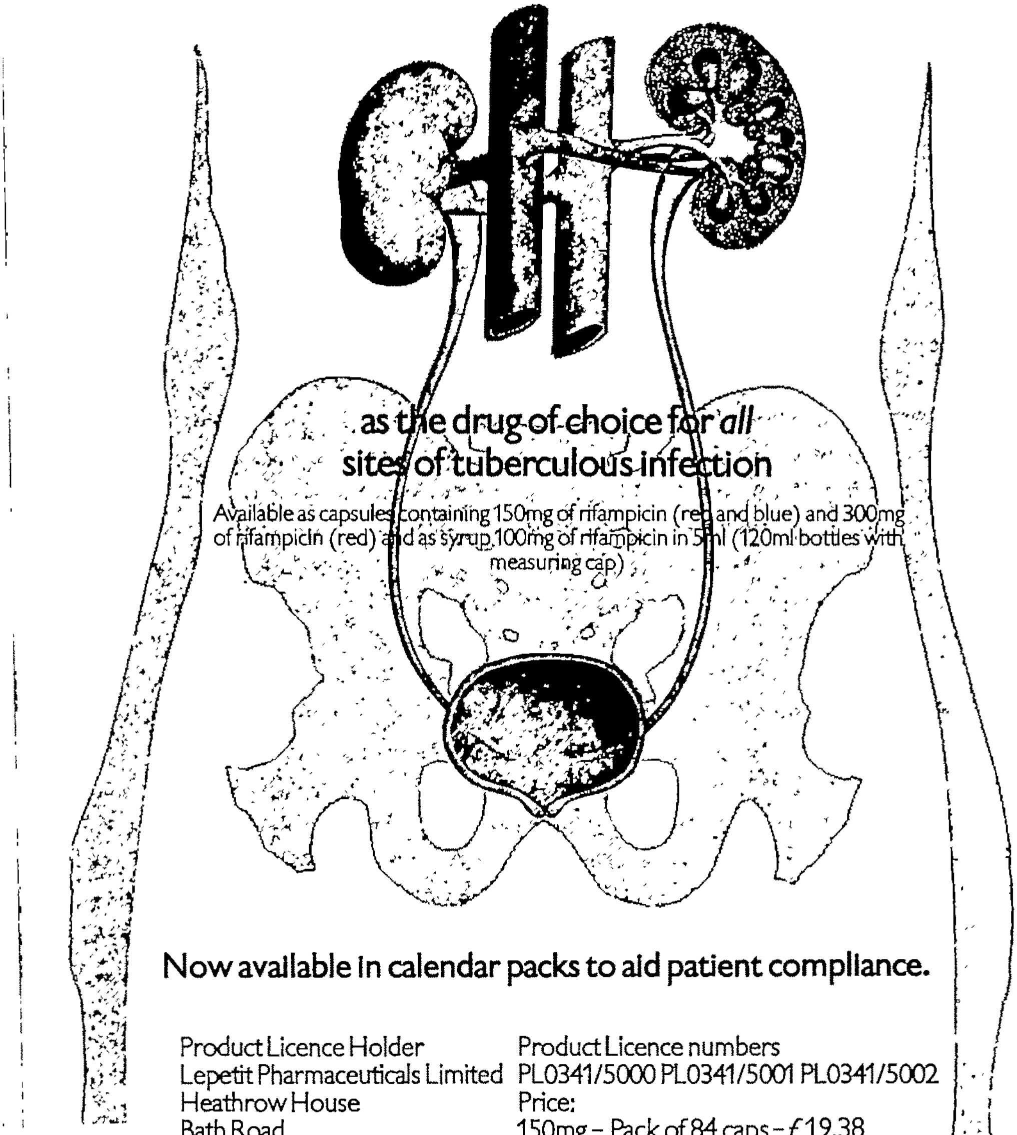

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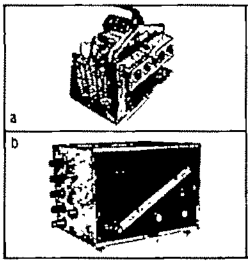

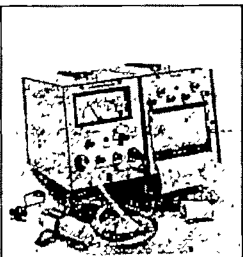

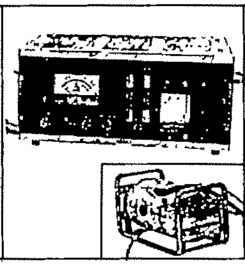

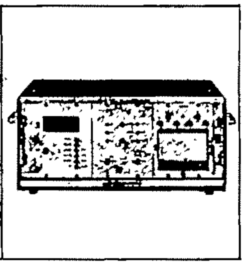

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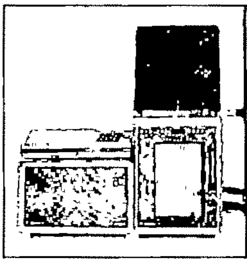

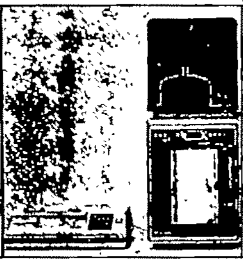

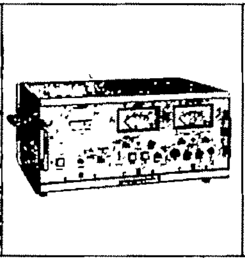

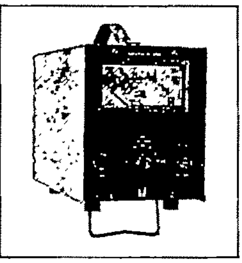

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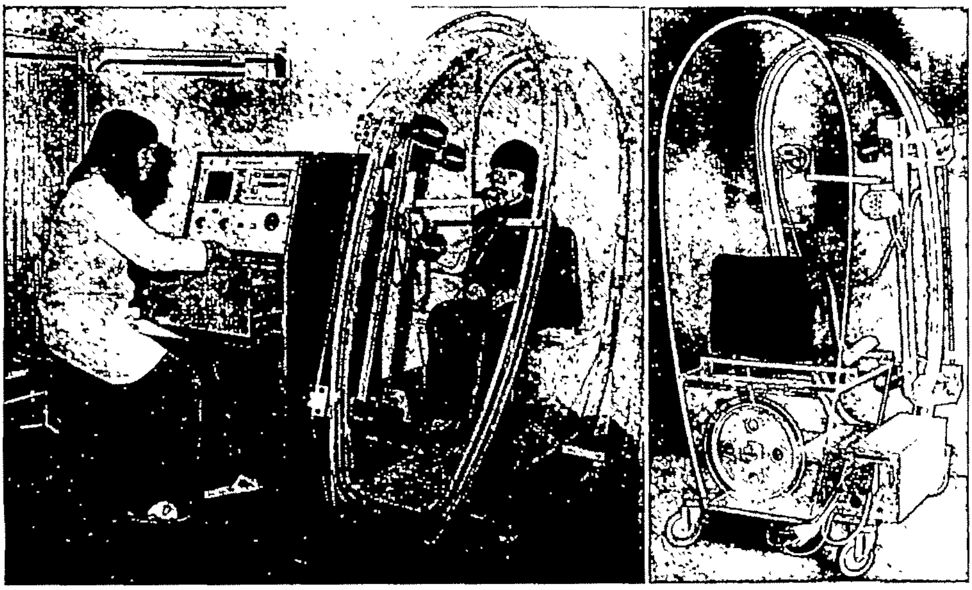

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HYPERCALCAEMIA AND HYPERCALCIURIA ASSOCIATED WITH PULMONARY TUBERCULOSIS

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Introduction

Hypercalcaemia and hypercalciuria are known to be associated with sarcoidosis but have rarely been described in patients with tuberculosis. We have recently treated a patient with pulmonary tuberculosis who suffered from transient hypercalcaemia and hypercalciuria at the onset of his illness.

Case Report

The patient, a 36-year-old Caucasian plumbing fitter, presented to the Royal Free Hospital in June 1977, complaining of lack of energy, together with a productive cough. Previously he had been a heavy smoker and heavy drinker although he had moderated both of these over the last year. In Ireland, 15 years ago, he had been in contact with tuberculosis. On examination, the patient looked well, but was pyrexial (37.5 °C). There were no other abnormalities apart from scattered crepitations anteriorly over the apex of the left lung. Further investigations revealed a haemoglobin of 17.3 g/dl and white blood count of 8.9×10^9/litre. Blood urea, electrolytes and liver function tests were normal. The results of calcium investigations were abnormal and are shown in Table I.

Table I. Results of calcium investigations

Date	*Serum calcium* (mmol/l)	*Inorganic phosphorous* (mmol/l)	*Albumin* (g/l)	*24-hour calcium excretion* (mmol)	*Parathormone* (ng/ml)
17 June 1977	2.61	0.9	63		
21 June 1977	2.73	0.92	46		
23 June 1977	2.67	0.98	48	10.9	
24 June 1977	2.56	1.00	49	10.2	
25 June 1977				9.0	
30 June 1977	2.58	1.00	47	5.8	
1 July 1977	2.45	1.33	49		
15 September 1977	2.11	0.86	43		0.15
Normal	2.1–2.6	0.8–1.4	35–50	2.5–7.5	0.15–1.5

Chest radiograph showed left upper lobe infiltration. Direct smear of sputum was positive for acid-fast bacilli. Culture yielded a fully sensitive *Mycobacterium tuberculosis*. Radiographs of hands and feet showed no evidence of hyperparathyroidism. On 21 June 1977, antituberculous chemotherapy was started, rifampicin 600 mg, isoniazid 300 mg, ethambutol 1600 mg daily, since when he has made clinical and radiological improvement.

DISCUSSION

Our patient suffered from hypercalcaemia and hypercalciuria which was found on routine biochemical screening. Clinically, we had not expected him to be hypercalcaemic although the chest radiograph appeared to show early calcific changes. This is of interest as hypercalcaemia *per se* can be a cause of pulmonary calcification (Murray 1977). Hypercalcaemia and hypercalciuria have rarely been described in association with pulmonary tuberculosis. In the earlier reports (Greisheimer & Van Winkle 1927; Kaminsky & Davidson 1931), fastive blood samples were not obtained and no attempt was made to avoid occlusion of the vein. These early reports were made whilst the patients were receiving cod liver oil or heliotherapy. Recent reports of hypercalcaemia in pulmonary tuberculosis are few (Shai et al. 1972; Sharma et al. 1972). It has been suggested that hypercalcaemia may be due to hypersensitivity to vitamin D, as is thought to be the case in sarcoidosis. Hypercalcaemia with bone tuberculosis has also rarely been recorded (Braman et al. 1973). In all these reports, as in this case, other causes of hypercalcaemia such as neoplastic disease, hyperparathyroidism, hyperthyroidism, milk alkali syndrome and Addison's disease were excluded as far as possible. Unfortunately, due to technical reasons, the parathormone level could not be measured during the patients hypercalcaemic episode, but it was normal when measured at follow-up. The mechanism for hypercalcaemia in tuberculosis is thought possibly to be the same as in sarcoidosis and indeed corticosteroids have been used with success in a single case of bone tuberculosis (Braman et al. 1973). However, it is worth noting that our patient's abnormal calcium metabolism returned to normal with antituberculous chemotherapy alone.

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UNUSUAL PRESENTATIONS OF PLEURAL SARCOIDOSIS

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Summary

Three patients with unusual patterns of pleural involvement by sarcoidosis are described. Two patients presented with massive recurrent pleural effusions and the third had extensive bilateral pleural thickening. Because of the uncommon presentations, the possibility of sarcoidosis in these patients was initially overlooked. The diagnoses were made only after extensive investigations including multiple biopsies.

INTRODUCTION

Pleural involvement by sarcoidosis has been increasingly recognized in recent years. The commonest presentation is a small, unilateral effusion in the presence of other pulmonary manifestations of sarcoidosis. The effusion may rarely be bilateral or massive or there may be pleural thickening with or without effusion. We report three patients with unusual manifestations of pleural sarcoidosis.

Case Reports

Case 1

This 27-year-old man had come from El Salvador three years ago. One year before admission he developed anorexia, malaise, fatigue, and weight loss of 10 kg. Six months before admission he became breathless on exertion and developed generalized lymph node enlargement. He denied night sweats or fever. He was admitted to another hospital where inguinal lymph node biopsy showed non-caseating granulomas. No tubercle bacilli were isolated from the lymph node or from numerous sputum samples.

Examination revealed firm, non-tender 2–3 cm lymph nodes in submandibular, anterior and posterior cervical, subclavicular, axillary and inguinal areas. Breath sounds were diminished at both bases. Cardiac examination was normal. Liver and spleen were not palpable.

Complete blood count was normal with the exception of 19% eosinophilia. Serum calcium was elevated at 3.4 mmol/litre (13.5 mg/100 ml). Tuberculin (5 TU) and coccidioidin skin tests were negative. Chest radiograph showed bilateral pleural thickening, bilateral interstitial infiltrates and hilar adenopathy. Right and left decubitus views did not demonstrate the presence of pleural fluid. Pulmonary function tests showed forced vital capacity of 2.4 litres (predicted 4.7), FEV_1 61% (83%), MMF 79 litres/minute (265), TLC 3.8 litres (6.2), FRC 2.1 litres (3.4), RV 1.2 litres (1.5) DLCO 14 ml/min/mmHg (29), coefficient of diffusion 5.2 ml/min/mmHg/litre (5.8), and estimated alveolar volume 3.0 litres (6.2). The normal coefficient of diffusion in the face of reduction in lung volumes is consistent with abnormalities due to pleural restriction rather than parenchymal disease.

He was treated with intravenous saline and oral prednisone 30 mg/day. By the tenth hospital day, serum calcium had fallen to 2.6 mmol/litre (10.4 mg/100 ml). Thoracentesis did not yield fluid. A pleural biopsy obtained with a Cope needle showed multiple non-caseating granulomas. Special stains and cultures of the tissue failed to reveal any bacteria, fungi or acid-fast organism.

Case 2

This patient was a 38-year-old Mexican man who was first seen with a five-month history of shortness of breath. A pleural tap was performed in Mexico but the results were not available. Antituberculous therapy (isoniazid and ethambutol) was begun 3½ months before admission. The patient remained dyspnoeic and developed fever, chills and weight loss of 6 kg. He discontinued therapy two weeks before admission to Los Angeles County USC Medical Center. Examination revealed a large right pleural effusion. Blood count was normal, Tuberculin (5 TU) and coccidioidin skin tests were negative. A chest radiograph showed a large right pleural effusion. Multiple sputum cultures were negative for tuberculosis and fungi. Thoracentesis yielded 700 ml of fluid with the characteristics of an exudate. Fungal and AFB cultures were negative. Coccidiomycosis complement fixation titres of serum and pleural fluid were negative. Pleural biopsies revealed chronic inflammatory changes. Thoracoscopic examination through a chest tube revealed whitish plaques on the visceral pleura, but biopsy specimens again showed only acute inflammatory changes. Six weeks after admission a right thoracotomy with decortication was performed. Biopsies of lung and pleura showed multiple non-caseating granulomas consistent with sarcoidosis or tuberculosis, but the latter was considered unlikely because of negative cultures of the lung and pleural tissues and the lack of response to antituberculous therapy.

Three years later the patient was without complaints, having received no therapy and the chest radiograph showed pleural thickening on the right.

Case 3

A 64-year-old Costa Rican woman developed dyspnoea on exertion, anorexia and night sweats. She was admitted to hospital in Costa Rica and given isoniazid and ethambutol although the diagnosis of tuberculosis was not substantiated. Continued weakness and shortness of breath led to admission to another hospital where a transbronchial biopsy showed non-caseating granulomas. Sputum and tissue cultures were negative for tuberculosis and fungi.

Her symptoms persisted and she was transferred to yet another hospital where a chest radiograph showed a large right pleural effusion. Investigations included negative ANF, LE preparation, and rheumatoid factor, normal angiotensin-converting-enzyme level, normal coccidioidomycosis and histoplasmosis complement fixation titres, and negative tuberculin skin test. Pleural fluid cultures did not grow any organisms. A pleural biopsy again showed non-caseating granulomas. Streptomycin and rifampicin were added to the therapeutic regimen but the pleural effusion continued to accumulate. An open lung biopsy was performed, and the specimens showed non-caseating granulomas. The patient was given prednisone and antituberculosis drugs were discontinued. The patient is doing well.

DISCUSSION

Nickerson (1937) documented pleural involvement by sarcoidosis for the first time in 1937 when he showed non-caseating granuloma in the pleura during an autopsy of a sarcoid patient. Tice and Sweany (1941) were the first to show that a pleural biopsy may reveal the presence of non-caseating granuloma in a patient with sarcoidosis. Since then several articles have appeared describing the occurrence of pleural disease in sarcoidosis (Chusid & Siltzbach 1974; Wilen et al. 1974; Sharma & Gordonson 1975; Beckman et al. 1976), but in more than 90 reported cases pleural thickening and massive effusions have been rare.

Tice and Sweany (1941), Everett and Overhalt (1968), and Nelson and Loudon (1973) reported four cases of pleural effusion and pleural thickening with biopsy confirmation. Wilen et al. (1974) reported nine cases of pleural thickening of which two were bilateral and four right-sided. One case was described as showing extensive pleural thickening and two progressed from pleural effusion to pleural thickening.

Case 1 is unusual because he presented with extensive bilateral pleural thickening in the absence of pleural effusion. There were no reasons to believe that he had had pleural effusion before his presentation to our hospital. To our knowledge dry Cope needle biopsy has not been used to detect non-caseating granuloma of pleura in sarcoidosis. The possibility of lymphoma was strongly considered in this patient because of his unusual presentation.

Massive pleural effusion has been reported infrequently. Berte and Pfotenhaver (1962), Everett and Overhalf (1968), and Chusid and Siltzbach (1962) presented one case each of massive pleural effusion in histologically proven sarcoidosis. Our Cases 2 and 3 each presented with a massive and recurrent pleural effusions which persisted despite repeated thoracentesis and drainage. Tuberculosis was erroneously diagnosed in both cases and both received prolonged courses of antituberculous therapy despite the lack of microbiological or histological evidence. The possibility of sarcoidosis was finally considered after the patients failed to improve.

The practice of giving antituberculous agents to patients with negative tuberculin skin test and exudative pleural effusion of unknown etiology is widespread in some parts of the world and Case 3 is such an example. This practice should be re-evaluated since the diagnosis of sarcoidosis may be entirely missed and the patients may be denied the opportunity for therapy with corticosteroids. Instead, such patients should be strongly considered for prompt pleural biopsy and open lung biopsy.

It is of interest that the level of angiotensin-converting-enzyme Case 3 was normal. Although this test has been said to be useful in the diagnosis of sarcoidosis, our experience demonstrates that only 50% of patients with acute sarcoidosis had significantly elevated angiotensin-converting-enzyme levels.

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BOOK REVIEWS

Mechanisms of Airway Obstruction in Human Respiratory Disease: Proceedings of the International Symposium, Tygerberg, 1978

M. A. de Kock, J. A. Nadel and C. M. Lewis

Rotterdam: Balkema. 1979. Pp. x+413. Price £21

This book is the published proceedings of a meeting held in Cape Town in March 1978. The scope of the symposium was broad and somewhat diffuse but the topics covered in most detail were: (1) airways· innervation, pharmacology and reactivity in human asthma and animal models of asthma; (2) newer methods for the analysis of airway and lung mechanics; and (3) epidemiology and attempts at clinical classification. Ten of the 28 chapters are written by South African workers, the remainder by well-known investigators from North America, Europe and Australia. Most chapters deal with the author's own recent work but the amount of detail presented varies greatly. Extensive discussion is included.

No one would expect such a book to provide a convenient or balanced 'state of the art' in such a wide field. Some of the authors have provided their latest, unpublished work with all its inconsistencies and problems and are in practice addressing fellow investigators. Others stand back from their work and present summaries of their current thinking. So the book is likely to be of most value to those who have special interests amongst the topics covered. Detailed chapters summarizing the author's recent work which I enjoyed included those on the relation of allergenic and non-specific bronchial reactivity (Hargreave), the analysis of the pressure–volume curve in airway obstruction (Colebatch) and De Kock's two chapters calling attention to the somewhat neglected role of the trachea and central airways. Macklem indicates, from a comparison of the response of both resistance and maximum expiratory flow to breathing helium–oxygen, why he now has reservations about helium flow–volume curves; he also provides a paper on peripheral airways obstruction in smokers and many useful points in the discussion. Ulmer discusses his provocative work on the site of the sensory receptors responsible for reflex bronchoconstriction. Useful summaries of their work are provided by J. B. Richardson on airway innervation and the possible role of non-adrenergic inhibitory nerves by Hogg on a primate model of asthma and by Nadel on the origins of hyper-irritability after viral infections or exposure to ozone. Other readers would no doubt select other chapters; clinical aspects are not neglected but there have been few recent developments in the problems of classification and definition. In short, this book has the familiar strengths and weaknesses of the book of a symposium. No one except editors and reviewers is likely to read the book right through but many will find sections of it interesting; a book to borrow for an hour or two but probably not to buy unless your budget is generous.

N. B. Pride

Lung Biology in Health and Disease, 11. Genetic Determinants of Pulmonary Disease

Stephen D. Litwin

New York: Marcel Dekker. 1978. Pp. xiv+218. Price $29.50

Geneticists are increasingly contributing to our understanding of lung disease. Newer epidemiological methods offer the hope of distinguishing genetic from environmental effects in large-scale surveys, and laboratory testing of HLA antigens and immune responses allow us to 'type' the individual. If immunological factors are important determinants of the expression of lung disease then, as those factors are genetically determined at least in mice, genetic factors should also be important in human disease.

This volume, like others in the series, offers a series of authoritative reviews. The first of seven chapters introduces basic concepts of modern genetics. The second deals with α_1-antitrypsin—its measurement, the complex typing system now used to study its genetics and the disorders associated with deficient tryptic activity. Chapter 3 gives a compact but useful review of cystic fibrosis and Chapter 4 covers other immune defects and their resulting lung disease. Chapter 5 deals with asthma and the unresolved problem of defining 'atopy', if such an entity exists in less nebulous terms than clinicians usually use when referring to skin prick test results. Chapter 6 reviews a handful of lung diseases with genetic factors, such as fibrosing alveolitis, and Chapter 7 covers Chronic Obstructive Pulmonary Disease (sic).

The book is beautifully produced and well written. It is extremely comprehensive, discussing the various diseases in detail covering clinical, pathological and physiological features as well as genetics. It will clearly be a useful source book for clinicians, especially those wanting brief but comprehensive accounts of the genetics of particular lung diseases. My only criticism would be of omission: nowhere are the pneumoconioses mentioned. The basic management of industrial lung disease is to prevent it; dust control is one method but defining susceptible subjects should be another aim. This is where geneticists can help by keeping workers out of the hands of doctors.

P. H. Wright

Roentgenologic Anatomy of the Lung

Hideaki Yamashita

Stuttgart: Georg Thieme. 1979. Pp. viii + 389. Price DM 248

In this extensive work the author has set out to detail the bronchial and vascular anatomy of the lungs. His aim is to improve radiological and endoscopic diagnosis and also to aid accurate subsegmental surgical procedures. With this in mind, the book has been divided into two sections. The first details the segmental and subsegmental anatomy based on dissections augmented by bronchographic and angiographic studies. In the second section, discussion of model experiments demonstrates the production of tomographic images. The pulmonary anatomy is then described by means of tomographic studies.

In part one, the anatomy of the bronchi and the vascular tree together with developmental variants are described in detail. It is perhaps a little surprising that normal measurements for the trachea and main bronchi are given on a series of only 10 patients. Measurements of segmental bronchi and blood vessels have been made on a larger series of up to 170 patients. The distribution of hilar and mediastinal lymph nodes is described only briefly. Illustrations of contrast studies of the airways and vascular tree of cadavers are beautifully enhanced by detailed diagrams. Whilst the anatomy of the major airways is of interest to radiologists and fibreoptic bronchoscopists, the detailed description at subsegmental level does not really have any great clinical significance. Unfortunately the quality of the reproduction of the radiographs makes the detailed anatomy difficult to visualize. It is not helped by the films being printed as postives (as opposed to the usual negative format). It is regrettable that the radiology of the lymph nodes has not been dealt with in more detail as this is critical to the spread of tumours. The absence of any correlation with CAT scanning is perhaps a surprising omission.

Whilst much work has clearly gone into the production of this book, it is felt that it will primarily be of interest to anatomists and that it does not have great clinical application. At the price, it is likely that its purchase will be confined to the larger libraries.

M. C. Pearson

Current Topics in Immunology, 10. Immunology of the Lung

Margaret Turner-Warwick

London: Edward Arnold. 1978. Pp. xii + 326. Price £14.95

This book is the tenth in this series under the general editorship of John Turk, and intended to provide for clinicians and those working in clinical laboratories brief accounts of the implications of modern immunology for their day-to-day work. In the past 25 years these have increased enormously. New knowledge and concepts and new techniques of laboratory and clinical investigation have been accompanied by increasing recognition of their relevance to a wide range of clinical problems. This now extends far beyond the limited fields of defence against infection and hypersensitivity reactions to such diverse topics as auto-immunity in the pathogenesis of many diseases of undetermined cause and histocompatibility antigens, not only in their obvious relevance to organ transplantation but also as markers of genetically determined variations in reactivity of the immune system.

Among established medical specialties, respiratory medicine has been particularly affected by these developments: not surprisingly, since the lungs are exposed continuously through the airways to antigens and infective agents in the respired air and through the circulation to potentially noxious factors in the total blood flow from all systemic organs. In respiratory medicine, immunology today seems to be in a position comparable to that of physiology 25 years ago. It is at the growing edge, where the accepted stories and even the terminology in which they are told are apt to change just as the clinician thinks he has achieved some understanding of them; and if the only way he can achieve this is by reading all the relevant original papers, he may well doubt whether the effort was worth while. His labour will be greatly reduced and he will be correspondingly encouraged by Professor Turner-Warwick's book, which provides a conspectus of the current position in immunology over the whole field of bronchopulmonary disease.

After brief accounts of those basic concepts of immunology that are relevant to the lung, and of the specialized procedures of skin, bronchial and nasal challenge tests, named diseases of known and of as yet unknown cause are considered. Lack of agreed terminology for some of these must have been frustrating in face of the need to present acceptable versions of several complicated stories in concise form. Professor Turner-Warwick minimizes or side-steps some of the difficulties by a pragmatic approach to definition. Thus, the chapter entitled Connective Tissue Disorders of the Lung with or without Necroting Angiitis includes a discussion of 'pulmonary eosinophilic exudates', but the relationship of these to the 'cryptogenic pulmonary eosinophilia' discussed in a previous chapter is left open. There is a useful chapter on defence mechanisms of the lung. The chapters on fibrosing alveolitis and on occupational diseases will be read with especial interest in view of the author's contributions to knowledge of the immunology of these conditions. The book ends with a brief discussion of the immunology of lung tumours.

The mass of factual information is agreeably leavened by interpretations of clinical phenomena, some in the present state of knowledge necessarily speculative. Many of these interpretations are set forth in the form of diagrams. These are admirable as a means of exposing hypotheses openly to criticism by the expert and to the possibility of refutation by experimental tests; but there is a danger that in spite of warnings, the uncritical student may accept them as representing established facts. The critical reader is unlikely to fall into this error, and will be helped in further study by ample bibliographies; to him this book can be warmly recommended.

J. G. Scadding

Chemoprophylaxis and Virus Infections of the Respiratory Tract, Volumes 1 and 2

J. S. Oxford

Cleveland, Ohio: CRC Press (Oxford: Blackwell Scientific). 1977. Pp. x+220 (vol. 1) and x+232 (vol. 2). Price £46.50 per volume

Amidst the euphoria of current virological success engendered by events such as the final eradication of smallpox virus and the disease it causes or the near comparable success with poliomyelitis, it is perhaps salutary to ponder on a virological failure. In this area the pride of place must go to our inability to make any meaningful impact on acute respiratory viral infection in spite of quite brilliant recent advances in the understanding of the causes and nature of these most common and troublesome complaints. Influenza vaccines are, of course, of some value but they are only relevant to part of the overall problem. It is not surprising therefore that hopes have been raised that these diseases might provide a suitable target for the rather sluggish science of antiviral chemotherapy.

The current state of play in this field is reviewed in these two attractively produced but very expensive volumes. It was perhaps courageous to produce this book at this time since it is admitted in the opening chapter that advance in this area is as yet inappreciable. The format is a series of chapters each written by a well-known authority on respiratory virology or some related speciality. The subject matter ranges widely to encompass general topics such as the clinical manifestations of infection, structure and mode of replication of the various viruses, animal model systems, commercial interests as well as the pharmacology and clinical evaluation of a handful of, at the moment, not particularly encouraging compounds. Indeed such is the breadth of the topics covered that the title is somewhat misleading; 'a textbook of respiratory virology with an emphasis on antiviral chemotherapy' would have perhaps have been more appropriate. Nevertheless, this is a very good text. The majority of the chapters are extremely well written and well referenced. Each of these is an excellent independent essay on its stated subject. This, however, does tend to result in some repetition; for example in Volume I, the structure of the virus was described in all four of the five chapters on influenza. From a clinical viewpoint there is perhaps one omission: an informed comment on the current practice of prescribing antibacterial substances for acute viral respiratory infections would have been valuable. It would not, however, have been easy to find a contributor to do this.

These volumes will be valued by all those with interest in respiratory viral disease but particularly those who for either academic or commercial reasons have faith that these diseases can be ameliorated by antiviral chemotherapy. Nevertheless, it must be appreciated that this is no *vade mecum* for practising physicians since there is, as yet, no effective therapy for these diseases.

R. B. HEATH

Pulmonary Pathophysiology: The Essentials

John B. West

Oxford: Blackwell Scientific. 1978. Pp. x+227. Price £7.50

It will be difficult for anyone to write a better, simpler or clearer account of clinical respiratory physiology than this and, on the maxim that it is wiser to know a small book well than a big book badly, I think every practising and would-be chest physician should know this book inside out and backwards and then re-read it regularly as a touchstone with reality. The book is a companion volume to John West's basic *Respiratory Physiology—The Essentials*. Reading it carefully, I found one unnecessary word 'asterixis' (flapping tremor), p. 160, but can make no other criticism. The book is in four sections, the first on functional tests, the second on diseased lungs, the third on respiratory failure and its treatment, and the fourth a series of factual appendices and self-examination questions. The illustrations are excellent.

DAVID DENISON

Lung Biology in Health and Disease, 12. The Lung in Transition between Health and Disease

Peter T. Macklem and Solbert Permutt

New York: Marcel Dekker. 1979. Pp. xxii+435. Price SFr 89

This is the twelfth volume in this series, and, like each of the other volumes, it is a notable book that repays very careful study. In particular it successfully sets out how little we know for certain, and how much needs to be determined, about the functional and pathological changes that accompany the early stages of common lung diseases. The editors have deliberately confined the work to studies of those conditions causing chronic airflow limitation, and all the contributors rely very heavily upon the differences between lungs of asymptomatic smokers and non-smokers as models of these states. As the book is written by 24 authors with none contributing to more than four of its sixteen chapters, there is considerable repetition of example and explanation but, since all of the contributors are internationally recognized and have very different ways of teaching, this is an advantage and not a failing.

The volume opens with an account, by David Bates, of what is actually observed clinically, the so-called 'natural history' of chronic bronchitis and emphysema. Its style is deceptively simple and betrays a very careful separation of wheat from chaff. Dr Thurlbeck continues with a description of the pathological changes that are seen, especially in the lungs of young smokers dying from other than pulmonary causes. His chapter contains many valuable references and lessons, for example, of the importance of avoiding the term 'early' when thinking of histological lesions, since there is no formal evidence that they are early or that they will continue.

Following these introductory chapters there are 14 others which are largely devoted to clinical and epidemiological studies using conventional or almost conventional tests of lung function, e.g. maximum mid- and late-expiratory flow rates, the slope of phase III, closing volumes, frequency-dependence of compliance, V/Q inequality, and so on. Without doubt these are splendid value, especially when they emphasize how much is surmise and how little is fact, as is to be expected from authors of such high calibre. However, sitting in their midst is a delightfully destructive time-bomb in the form of Donald Proctor who asks 'are we currently directing an excessive effort towards the development and interpretation of pulmonary function tests, and too little investigative effort into the underlying physiology and pathology affecting that function?' Later in his chapter on Tests of Airway Defence Mechanisms is the refreshing comment that 'Chest Physicians and respiratory physiologists have in large part traditionally ignored the upper airway. Indeed they have gone so far as to utilize the term to describe the major tracheobronchial tree, a usage only applicable to the decapitated subject'.

In the face of so many good things it seems mean to carp at minor failings, but some strike through, largely due to poor proof reading. For example 'readiologic' (p. 23), 'comprensation' (p. 44), 'effort dependent' instead of 'effort independent' (p. 44), the contradictory statements 'can only limit' and 'cannot limit' (p. 49), and 'disturbution' (p. 197), but doubtless these will be corrected in the next printing. Two criticisms of slightly more substance suggests themselves. Firstly, there is no mention of the additional information that can be obtained from maximal flow volume curves if the inspiratory limb is also recorded. Secondly, Menkes and Permutt, in a very stimulating analysis of the temporal characteristics of expirograms, draw an analogy between the transit times of dye molecules injected as a bolus into venous blood travelling to the lung and the transit times of expired gas molecules leaving the alveoli, and I am not sure that this analogy is justifiable or necessary to their argument, but developing a case against it would fill another page.

Altogether, this book is an exciting addition to a very good series.

DAVID DENISON

Tutorials in Postgraduate Medicine, 5. Respiratory Disease

D. J. Lane

London: Heinemann Medical. 1977. Pp. xvi + 565. Price £12.50

This excellent book provides a most clear synthesis between theory and clinical practice of respiratory medicine. In the first section on theory the editor has brought together authorities such as Professor Turner-Warwick, Professor Thurlbeck, Professor Widdicombe and Dr Muir to write on the basic functions of the lung. I particularly liked the clear explanation of gas exchange by the editor and the comprehensive description of the exocrine secretory function of the lung by Professor Thurlbeck.

A second section includes chapters on common clinical disorders. Amongst these was a particularly useful chapter on the chest radiograph and interpretation of widespread shadowing by Professor Turner-Warwick. The final section on selected topics has two valuable chapters for the physician on the respiratory aspects of anaesthesia and on surgery for non-malignant pulmonary disease.

A truly splendid book and a must for all postgraduates interested in respiratory medicine.

T. HIGENBOTTAM

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References: 1 Chemotherapy (1977), 23, 58-64. 2. Drugs (1975), 9, 81-140. 3. J. Infect. Dis. (1977), 135, 999-1002. 4. Brit. med. J. (1976), 2, 1407. 5. Brit. med. J. (1972), 3, 13-16.

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THE BRITISH THORACIC ASSOCIATION

A meeting was held at the Royal Free Hospital, London, on 31 January and 1 February 1980, in conjunction with the Thoracic Society. The following papers were presented; abstracts of these papers will be published in *Thorax 35*, 222.

Carcinoma of the bronchus: incremental factors affecting prognosis *by M. Azariadis, R. K. Firmin, A. Rees, M. Paneth, C. R. Lincoln and S. C. Lennox*, Brompton Hospital, London

Preoperative radiotherapy and surgery in the treatment of oat cell carcinoma of the bronchus *by V. Levison*, North Middlesex Hospital, London

Carcinoid tumours of the lung *by R. Hurt*, North Middlesex Hospital, London

Dermoid cysts of the mediastinum *by J. Southgate and P. R. Slade*, Groby Road Hospital, Leicester

Alveolar cell carcinoma: clinical, radiological and pathological correlations *by A. M. Hunter, R. M. E. Seal and B. H. Davies*, Sully Hospital, Glamorgan

Some observations on the surgical treatment of oesophageal cancer *by H. V. Wingfield*, Tehidy Hospital, Camborne, Cornwall

Emergency open-heart surgery: experience with 100 consecutive cases *by F. C. Wells, D. K. C. Cooper, B. Milstein and T. English*, Papworth Hospital, Cambridge

Bronchial artery ligation in the treatment of major haemoptysis, *by R. Franks, S. Williams, O. S. Tubbs and S. C. Lennox*, Brompton Hospital, London

Thrombotic obstruction of Bjork-Shiley valves *by S. A. Photiou, D. L. Cheung, M. J. Drakeley, J. L. Mercer and J. B. Meade*, Broadgreen Hospital, Liverpool

Scanning electron microscope appearances of glycerol-preserved allogenic dura matter before and after implantation into patients *by M. A. Glasby, A. J. Gunning, M. Jenkins, I. Mustafa and M. H. Yacoub*, John Radcliffe Hospital, Oxford

Plasma CEA measurements in the preoperative assessment of lung cancer *by T. C. Stokes, J. Stevens, P. Long, J. R. Belcher and A. L. Miller*, The London Chest Hospital

Oesophagectomy in patients with oesophageal speech *by D. T. C. Watson, J. Hadley, J. C. Marsh and H. R. Matthews*, Queen Elizabeth Hospital, Birmingham

Transit time analysis of the forced expiratory spirogram in male smokers *by D. P. Osmanliev, E. E. Davies and N. B. Pride*, Royal Postgraduate Medical School, London

Transit time and derivatives as guides to the reversability of chronic airflow obstruction *by R. Bellow, M. J. Campbell, G. Collins, J. E. Cotes and D. R. Tagaro*, Pneumoconiosis Unit, Llandough Hospital, Glamorgan

Partial expiratory flow-volume curves and their use in measuring bronchodilator responses in normal subjects *by H. R. Gribbin, P. J. Barnes and N. B. Pride*, Hammersmith Hospital, London

The reproducibility of flow rates measured with low-density gas mixtures for assessing airways obstruction *by I. S. Petheram, C. W. Bierman, J. Moxham and S. G. Spiro*, University College Hospital, London

Respiratory muscle function and fatigue: studies on the sternomastoid *by J. Moxham, S. G. Spiro, C. M. Wiles and R. H. T. Edwards*, University College Hospital, London

Pain relief after thoracotomy *by J. R. Wedley*, Guy's Hospital, London

Bronchoscopic assessment of tracheal damage following endotracheal intubation *by D. Honeybourne, C. Barham, J. F. Costello and L. Strunin*, King's College Hospital, London

Lung folding simulating peripheral pulmonary neoplasm (Blesovsky's syndrome) *by C. R. Payne, P. Jacques and I. H. Kerr*

Cough versus chest physiotherapy in the regional clearance of excessive tracheobronchial secretions *by J. R. M. Bateman, S. P. Newman, K. M. Daunt, F. Nóirín, D. Sheahan, D. Pavia and S. W. Clarke*, Royal Free Hospital, London

The effect of an extension tube on the bronchodilator efficacy of terbutaline delivered from a metered dose inhaler *by N. P. Keaney, S. A. Gomm, N. J. P. Winsey and T. B. Stretton*, Manchester Royal Infirmary

Pigeon bloom: a further antigen in pigeon breeder's disease *by H. MacKenzie, C. McSharry, P. Lynch, S. W. Banham and G. Boyd*, Glasgow Royal Infirmary

Do carcinoid tumours of the trachea occur? *by R. K. Firmin, B. Heard, A. Dewar and S. C. Lennox*, Brompton Hospital, London

Serial pulmonary function tests in SLE *by P. W. Ind, H. R. Gribbin, J. M. B. Hughes, K. B. Elkon and J. R. Sewell*, Hammersmith Hospital, London

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FUTURE MEETINGS OF THE BTA

The list below gives details of future meetings, both arranged and provisionally planned, and we hope this will prevent the clashing of dates with meetings arranged by other societies.

9–11 April 1980	Jointly with the Welsh Thoracic Society. University of Swansea.
3–6 September, 1980	Jointly with the Norwegian Thoracic Society. Lillehammer, Nr. Oslo, Norway. The cost will be approximately £22 per day for full pension. It is hoped to negotiate a cheaper rate for members wishing to stay a week.
January/February 1981	Jointly with the Thoracic Society. Royal Free Hospital, London. A two-day meeting.

6–9 May 1981	Jointly with the Europe Region International Union Against Tuberculosis and the Chest, Heart and Stroke Association, Bournemouth.
January/February 1982	Jointly with the Thoracic Society. A two-day meeting at the Royal Free Hospital, London.
30 June–3 July 1982	Jointly with the Thoracic Society, University of York.
27–30 June 1983	Churchill College, University of Cambridge.
24–27 June 1985	Churchill College, University of Cambridge.

Further details of these meetings can be obtained from Dr G. Anderson, Newport Chest Clinic, 129 Stow Hill, Newport, Gwent NPT 4GA.

FUTURE MEETINGS OF THORACIC SOCIETY

3–4 July 1980	Summer Meeting, Durham University.
January/February 1981	Jointly with the BTA. A two-day meeting at the Royal Free Hospital, London.
4–5 July 1981	Jointly with Scottish Thoracic Society. St Andrews University.
January/February 1982	Jointly with the BTA. A two-day meeting at the Royal Free Hospital, London.
30 June–3 July 1982	Jointly with the BTA, York University.

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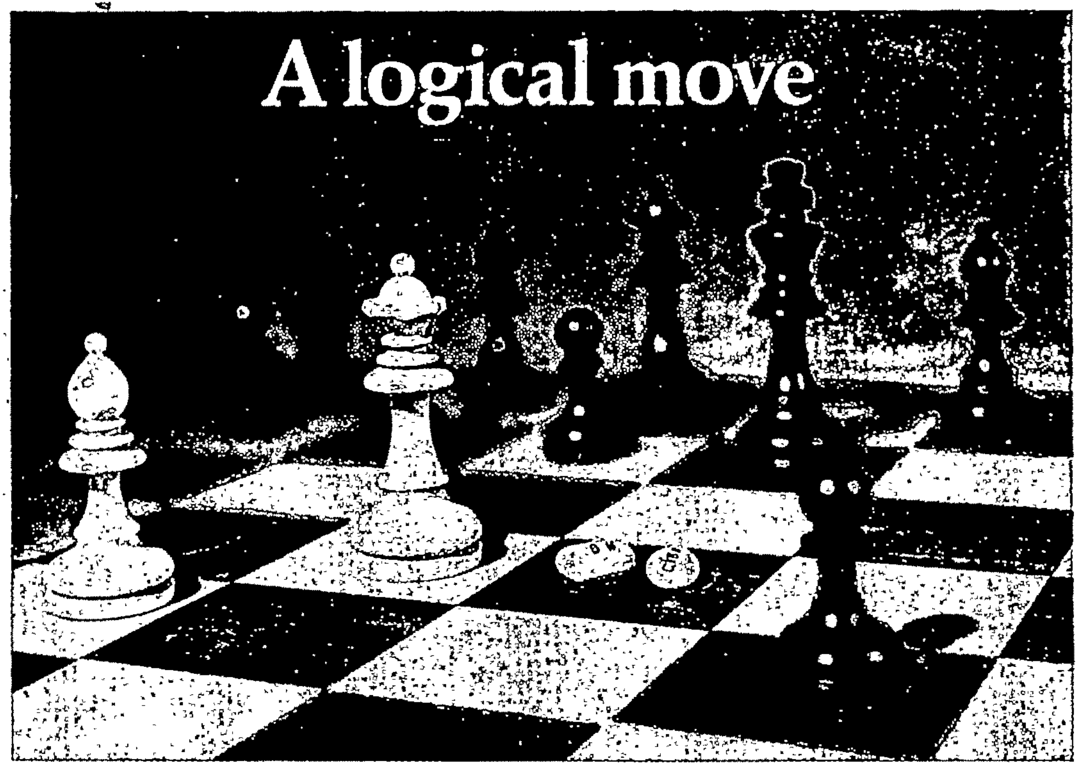
The British Thoracic Association invites papers for presentation at the Joint Meeting with the Norwegian Thoracic Society on 3–6 September, 1980, at Lillehammer, Nr. Oslo, Norway. Summaries of 200–300 words should be submitted to the Honorary Secretary, Dr G. Anderson, Newport Chest Clinic, 129 Stow Hill, Newport, Gwent NPT 4GA by 1 May 1980.



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EFFECTIVENESS OF BCG VACCINATION IN GREAT BRITAIN IN 1978

A REPORT FROM THE RESEARCH COMMITTEE OF THE
BRITISH THORACIC ASSOCIATION*

Summary

BCG vaccination of older school-children in Britain continues to offer more than 70% protection against tuberculosis for at least ten years after vaccination.

In England and Wales between 1973 and 1978 the tuberculosis notification rate in tuberculin-negative unvaccinated life-time residents aged 15–19 years fell by 50%. There was no change in rate for those given BCG vaccination, possibly because of less satisfactory techniques of vaccination in some areas.

It is estimated that for life-time residents of England and Wales BCG vaccination of 100 000 older school-children in 1978 will prevent about 44 notifications in the 15 years following vaccination.

INTRODUCTION

Previous studies have given evidence of the protective effect of BCG vaccination in adolescents in England and Wales, both in a controlled trial (Hart & Sutherland 1977) and in routine use (British Thoracic and Tuberculosis Association 1975). Because of the decline in annual infection risk indicated by a tuberculin survey (Christie & Sutherland 1976) the possibility has been considered that the time might be approaching when the national policy of routine BCG vaccination for all older school-children (aged 10–13 years) should be reviewed (Stilwell 1976; Springett 1976). This paper provides further estimates of the contribution made by the schools BCG scheme in recent years, but does not attempt to formulate policy.

In addition to ascertaining the present effectiveness of BCG vaccination given under routine conditions, the present study has two further objectives. One is to measure the effectiveness of BCG over a longer period after vaccination than in the British Thoracic and Tuberculosis Association study in 1973 (published in 1975). The other is to test the hypothesis that tuberculosis due to recent infection is declining at about the same rate as has been shown for the annual risk of infection. The opportunity was also taken to extend the survey area to the whole of Britain by including Scotland as well as England and Wales.

To achieve the first of these objectives the age range covered in 1978 was extended from 15–19 years as in 1973 to 15–24 years. As a result the group studied at age 20–24

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*The survey was carried out by a subcommittee of the Research Committee of the British Thoracic Association, whose members were: J. H. Angel (*Chairman*), V. H. Springett (*Coordinator*), C. A. C. Pickering and I. Sutherland. The report was prepared by V. H. Springett and I. Sutherland.

years in 1978 represents the same cohort as had been studied at age 15–19 years in 1973; hence the protective effect of vaccination can be studied in the cohort for a further five-year period.

The second objective may be achieved, at least in part, by a comparison of the notification rates of BCG-vaccinated and tuberculin-negative unvaccinated groups aged 15–19 years in 1973 and 1978. The development of tuberculosis in these groups at this age must depend closely on the risk of infection, and the change in the incidence of the disease should therefore correspond approximately to the change in the risk of infection.

Methods

The method was similar to that used in 1973. The cooperation of chest physicians throughout the country was first sought and a high proportion agreed to participate. They were asked to complete a survey form for each person in the 15–24 age group notified as suffering from tuberculosis during 1978 and to return the form to the coordinator. In addition to particulars of identification and the localization of tuberculosis, the form was designed to record the tuberculin/BCG history, with special reference to the schools BCG scheme; the result of the tuberculin test or the fact of BCG vaccination was confirmed from contemporary records if possible. For those who had had BCG, information was also requested on the presence or absence of a scar at the vaccination site. For immigrants who first entered Britain when aged 15 years or more only the date of entry to Britain was required, since they could not have been included in the schools BCG scheme.

Some weeks after the end of each quarter of the year the coordinator received tables from the Office of Population Censuses and Surveys and from the Information Services Division of the Scottish Home and Health Department showing the number of notifications in the age group for each sex, and for respiratory and non-respiratory tuberculosis for each administrative district. The number of survey forms received from each district was compared with the number in the table, and if necessary a reminder letter with further forms was sent to the chest physician concerned.

At the end of the year, when the final total of notifications for each district was known, a list of names of the persons for whom forms had been received was sent to each chest physician, asking for information on the results of bacteriological investigations or any revision of diagnosis.

By relating the numbers of notifications in the various groups to the corresponding population (see below), notification rates were obtained or estimated for the BCG-vaccinated and for the unvaccinated tuberculin-positive and tuberculin-negative groups.

RESULTS

Population estimates

The tuberculosis notifications analysed in this report are those occurring among the population who were aged 15–24 years in 1978 and who had been resident in Great Britain at age 13 years (when BCG vaccination is offered in most schools). In some areas BCG is offered at a slightly younger age, but this is not of major importance. The required total population has been obtained from the Registrar General's estimates of the numbers of persons aged 13 years on 30 June each year from 1967 to 1976 (Office of Population Censuses and Surveys 1975, 1977, 1979). The population aged 15–24 years in 1978, resident since age 13 years, is thus estimated at 8080 000. No allowance has been made for death or emigration from Great Britain between age 13 years and 1978, because the numbers involved are not large and will not have materially altered the proportions of this population cohort according to skin test and vaccination status.

The subdivision of this total according to status at age 13 years in relation to the schools BCG vaccination scheme has been made as follows:

1. The local authority returns to the health departments for school-children and students show that 5630 000 were given BCG in the years 1967–76; this total includes a relatively small number of vaccinations of students at older ages, which cannot be separated, but does not include vaccinations of contacts. During the same period a further 639 000 were found to be tuberculin-positive and were not vaccinated.

2. The balance of 1811 000 ostensibly consists of non-participants in the scheme. However, they include a small number who were found to be tuberculin-negative in the scheme but were not vaccinated. Scrutiny of the detailed returns for England and Wales in 1976 suggests that the proportion of tuberculin-negative children escaping vaccination is close to 1%. This leads to an estimate of 57 000 found to be tuberculin-negative in the schools scheme but not vaccinated.

3. In addition, some of the non-participants will have been outside the scope of the scheme because they had already been found to be tuberculin-positive or had been given BCG before age 13 years, usually as contacts. The local authority returns of the numbers vaccinated as contacts are not subdivided by age, nor is there any routine record of the numbers of contacts found to be tuberculin-positive when tested. In the British Thoracic Association contact study (British Thoracic Association 1978), carried out in 37 chest clinics in Britain in 1973–4, 71% of 1156 unvaccinated close contacts with grade 0 or 1 Heaf test reactions were aged under 15 years, and 24% of 662 unvaccinated close contacts aged 5–14 years were found to have grade 2 or greater Heaf test reactions. On the basis of these figures it has been assumed that 75% of those vaccinated in Britain as contacts were under 13 years and that 25% of all the contacts tested under this age were tuberculin-positive. Applying these percentages to the total numbers vaccinated as contacts in the years 1967–76 from the local authority returns, those found to be tuberculin-positive prior to age 13 years are estimated to be 126 000 and those given BCG before age 13 years to be 379 000. After subtracting these two estimates (and the estimate in the previous paragraph) from the non-participants, there remain an estimated 1249 000 who, though eligible, did not participate in the scheme.

4. Finally, it has been assumed that the proportion of these non-participants who were tuberculin-positive was the same as among the participants in the scheme. This leads to estimated totals of 124 000 tuberculin-positive non-participants and 1125 000 tuberculin-negative non-participants in Great Britain. The accuracy of this assumption is surprisingly not of critical importance; even if the proportion of tuberculin-positives in non-participants is assumed to be twice that in participants the estimates of the effectiveness of BCG remain almost the same.

Population estimates on the same basis have been calculated separately for the two five-year age groups 15–19 and 20–24 and also separately for England and Wales.

Notifications

Table I shows that the survey forms were received for 1269 (77.5%) of the 1638 persons aged 15–24 years notified as suffering from tuberculosis in Great Britain in 1978. The proportion of forms received was similar for Scotland (79.5%) and for both the 15–19 year age group (78.3%) and the 20–24 year age group (76.7%) in England and Wales.

The proportion of forms received was lower for non-respiratory tuberculosis (60%) than for respiratory tuberculosis (85%).

There were 648 forms for immigrants who entered this country after the age at which BCG is given in most schools and they had not therefore been available to take part in the scheme. The proportion of immigrants entering after school age was much lower for Scotland (8%) than for England and Wales, where the proportion was lower (35%) in the 15–19 year age group than in the 20–24 year age group (66%).

Also shown in Table I is a total of 72 who had not been eligible for the schools BCG scheme because of events before the usual age for vaccination. Six had had tuberculosis, 27 had had a positive tuberculin test and 39 had had BCG vaccination.

Table I. Great Britain 1978, persons aged 15–24 years. Notifications of tuberculosis and survey forms received

Notifications of tuberculosis		1638	
Survey forms received		1269	(77.5%)
Eligible for schools BCG scheme		511	
BCG vaccinated	212		
Tuberculin +ve	109		
Non-participant	190*		
Not eligible for schools BCG scheme		720	
Tuberculosis, tuberculin +ve or BCG *before* age 13 years	72		
Immigration *after* age 13 years	648		
Wrong age, year or diagnosis, and duplicate notifications		38	

*Includes ten found tuberculin-negative but not vaccinated.

There were an additional 38 forms which were not included in the main analysis, nine because the original diagnosis of tuberculosis had been revised, eight because they represented duplicate notifications and 21 because of errors of classification of age or of year of notification.

There remain 511 forms for persons who had been eligible for the schools BCG scheme: 212 had received BCG vaccination, 109 had been found tuberculin-positive and 190 had not participated in the scheme, including ten who had had a negative tuberculin test but had not had BCG vaccination. Table II summarizes some features of these three groups.

The fact of BCG vaccination was confirmed from the original records for 61%. In those aged 15–19 years confirmation was obtained for 79%, but in those aged 20–24 years confirmation was possible for only 45%, mainly because of the destruction of the records at varying intervals after school-leaving age. A scar at the site of vaccination was recorded for 90%, no report being made for most of the remainder.

The proportion with confirmation of a positive skin test is higher at 75% and again the proportion confirmed from the records is greater in the younger age group, 83% compared with 58%. The higher proportion confirmed in positives is probably related to the fact that in many areas positive results are reported to the chest clinic, where the record is held for longer than in the immunization records.

The proportion of the non-participants in whom it could be confirmed that BCG had not been administered is much lower, mainly because of the inherent difficulty of confirming a non-event. Confirmation was possible only in special circumstances, such as active refusal of permission by the parent. The more common reasons such as absence from school (which may have been intentional) were not confirmed.

Table II. Comparison of survey groups

	Classification in schools BCG scheme					
	BCG vaccinated		Tuberculin +ve		Non-participant	
	No.	%	No.	%	No.	%
Total	212	100.0	109	100.0	190*	100.0
Classification in schools scheme confirmed from original record	130	61.3	82	75.2	35	18.4
Not confirmed, BCG scar	62	29.2	—		—	
Not confirmed, no scar	20	9.4	—		—	
Tuberculosis confirmed by bacteriology or histology	107	50.5	52	47.7	78	41.1
Negative bacteriology	49	23.1	36	33.0	66	34.8
No information on bacteriology	56	26.4	21	19.3	46	24.2
Born in						
Great Britain	163	76.9	53	48.6	146	76.8
Asia or Africa	38	17.9	52	47.7	30	15.8
Rest of world	11	5.2	4	3.7	14	7.4
Non-respiratory tuberculosis	30	14.2	22	20.2	15	7.9
Males	93	43.9	52	47.7	90	47.4
Females	119	56.1	57	52.3	100	52.6
Age 15–19 years	101	47.6	76	69.7	90	47.4
Age 20–24 years	111	52.4	33	30.3	100	52.6

*Includes ten found tuberculin-negative but not vaccinated.

Evidence of confirmation of the diagnosis of tuberculosis by bacteriological or histological findings was reported to the survey in less than half the cases. These low figures are partly due to the fact that results, even when available, were not always reported to the coordinator. The highest proportion of confirmed diagnoses was in the BCG-vaccinated group, which suggests that if anything this group may have been subjected to more stringent standards of diagnosis than the other groups.

Amongst this group of persons who were aged 15–24 years when notified in 1978 and who were resident in Great Britain when aged 13 years, the proportion of immigrants before the age of 13 years was much higher in the tuberculin-positive group (51%) than in the BCG vaccinated group (23%) or the non-participants (23%). This larger proportion of immigrants among the patients most probably reflects a larger proportion of immigrants in the relatively small tuberculin-positive population than in the vaccinated and non-participant populations.

Non-respiratory tuberculosis occurred in a higher proportion of patients who were tuberculin-positive than in the other two groups, probably because of the higher proportion of immigrants in this group. In all groups there were slightly more notifications of females than of males.

In the BCG vaccinated and non-participant groups just under half the notifications were in the 15–19 year age group, with a slightly larger number at age 20–24 years. In contrast to this there were many more notifications at age 15–19 years than at age 20–24 years in the tuberculin-positive group. This reflects the relatively high incidence in the first few years after primary infection in the 15–19 year age group, whereas the 20–24 year age group are known to have been positive for at least seven years.

Table III. Great Britain 1978. Persons age 15–24 years. Estimation of notification rates in survey groups

Classification in schools BCG scheme	*Population* (*a*)	*Survey returns* (*b*)	*Notification rate* (per 100 000)	
			$c=\frac{b}{a}\times 100\,000$	$d=c\times\frac{100}{77.5}$
BCG-vaccinated	5630 000	212	3.77	4.86
Tuberculin-positive	639 000	109	17.06	22.01
Non-participant, not previously tuberculin-positive or vaccinated	1249 000	180	—	—
Estimated tuberculin-positive	124 000	21.2 ←	17.06 ←	—
Estimated tuberculin-negative	1125 000	158.8	—	—
Tuberculin-negative, not vaccinated	57 000	10	—	—
All negative not vaccinated	1182 000	168.8	14.28	18.43
Protective effectiveness			74%	

c—based upon reported notifications.
d—corrected to allow for under-reporting (see text).

Notification rates

From the population given BCG vaccination and the number of notifications in the BCG vaccinated group a notification rate can be calculated for BCG vaccinated subjects, as shown in the first line of Table III. The rate (*c* in Table III) based on notifications reported to the survey is 3.77 per 100 000, and this is multiplied by 100/77.5 to allow for under-reporting to give a rate (*d* in Table III) representing all the notifications in Great Britain in vaccinated subjects of 4.86 per 100 000.

The notification rate for those found to be tuberculin-positive at school can also be calculated directly. As shown in line 2 of Table III it is 17.06 per 100 000 for notifications reported to the survey, increased to 22.01 per 100 000 when allowance is made for under-reporting.

A rate for all non-participants could be calculated similarly, but is of little interest. The population of non-participants has been divided into tuberculin-positives and tuberculin-negatives on the assumption that they occur in the same proportion as in the tuberculin tested participant group. (As explained above, this is not a critical assumption.) If it is further assumed that the notification rate observed in the tuberculin-positive group applies also to this estimated positive group, then the number of notifications in the group can be estimated. Subtracting this number from the total of notifications in non-participants gives the number of notifications in estimated tuberculin-negative non-participants and thus a rate for tuberculin-negative non-participants can be calculated after adding both population and cases for the small group found tuberculin-negative but not vaccinated. The rate so obtained for tuberculin-negatives is 14.28 per 100 000 or 18.43 after allowing for under-reporting.

Table IV.-England and Wales. Estimated notification rates per 100 000 corrected for under-reporting

	1973	1978	
	Age 15–19	Age 15–19	Age 20–24
BCG vaccinated	3.7	3.8	5.2
Tuberculin-positive, not vaccinated	40.9	37.9	11.9
Tuberculin-negative, not vaccinated	28.5	12.3	21.8
No. of cases	243	211	198
Protective effectiveness	87%	69%	76%

Table V. Scotland 1978. Estimated notification rates per 100 000 corrected for under-reporting

	Age 15–19 *years*	*Age* 20–24 *years*
BCG vaccinated	8.3	7.8
Tuberculin-positive, not vaccinated	12.4	15.2
Tuberculin-negative, not vaccinated	35.9	65.2
No. of cases	39	40
Protective effectiveness	77%	88%

These calculations have also been carried out separately for the two five-year age groups, separating the results for England and Wales from those for Scotland. The results from the 1973 study of persons aged 15–19 years in England and Wales have been recalculated on the same basis, including the use of revised population estimates. The notification rates so obtained and corrected for under-reporting are shown for the three main survey groups in Table IV for England and Wales, and Table V for Scotland, but without showing all the steps of the calculation.

Notification rates for life-time residents of England and Wales

As indicated previously, the survey notifications for England and Wales include a substantial proportion (34%) of immigrants, a group in which the notification rate is known to be much higher than in the rest of the population (British Thoracic and Tuberculosis Association 1973). Place of birth is recorded on the survey forms, so that the number of notifications of life-time residents of England and Wales can be counted separately.

From the 1971 Census estimates have been made of the population of life-time residents of England and Wales aged 13 years in the years 1967–76. By relating the corresponding survey notifications to this population, notification rates for life-time residents are obtained as shown in Table VI. The proportions given BCG, found tuberculin-positive and not participating are assumed to be the same in life-time residents as in the total population. In the population as a whole the proportion of immigrants before the age of 13 years is so small (4%) that the inaccuracies involved cannot seriously affect the estimate.

Table VI. England and Wales. Estimated notification rates per 100 000 life-time residents, corrected for under-reporting

	1973	1978	
	Age 15–19	Age 15–19	Age 20–24
BCG vaccinated	2.5	2.6	4.2
Tuberculin-positive, not vaccinated	17.7	14.1	7.6
Tuberculin-negative, not vaccinated	21.1	10.5	17.4
Number of cases	145	127	149
Protective effectiveness	88%	76%	76%

It is, however, impossible to make reliable estimates of the size of the immigrant population, or of the proportions who were vaccinated, found positive or did not participate in the schools BCG scheme. Therefore no attempt has been made to assess the effectiveness of BCG vaccination in immigrants.

Protective effectiveness

The protective effectiveness of BCG vaccination is the percentage reduction in notification rate in the BCG vaccinated group compared with the tuberculin-negative unvaccinated group. For the 15–24 age group in Great Britain, including immigrants before the age of 13 years, this is

$$\frac{100(18.43-4.86)}{18.43} = 74\% \text{ (Table III)}$$

In each sub-grouping by age, calendar year, geography or place of birth shown in Tables IV, V and VI the protective effectiveness is never below 69% and in two subgroups is as high as 88%.

The protective effectiveness is at about the same level in Scotland as in England and Wales, though the number of cases for analysis is rather small. The protective effectiveness in England and Wales in the cohort aged 15–19 years in 1973 and 20–24 years in 1978 is only slightly affected by removing the immigrant population, but for the cohort aged 15–19 years in 1978 the estimated protective effectiveness is increased from 69% to 76% if immigrants are excluded.

DISCUSSION

This study has given two important results: first, that in the year 1978 the schools BCG vaccination scheme continued to give at least 69% protection in those aged 15–19 years who had been given BCG vaccination at school; secondly, that this level of protection is continued for at least a further five years from vaccination to cover the group aged 20–24 years in 1978.

The other main objective of this study was to assess changes in notification rates between 1973 and 1978, especially in the tuberculin-negative and BCG-vaccinated groups, as indicators of change in the infection rate. To achieve this, the actual rates in these groups must be compared in the two years. To make the comparison as precise as possible this needs to be done for life-time residents of England and Wales only; Scotland was not included in the 1973 study. The restriction to life-time residents is necessary because of the much higher notification rates in immigrants, as a result of which even relatively small changes in the proportion of immigrants could lead to appreciable changes in the rates under study.

For convenience, the rates in Scotland in 1978 are first compared with those in England and Wales. The changes in the rates in life-time residents of England and Wales between 1973 and 1978 are then considered.

Notification rates in Scotland and in England and Wales in 1978

For tuberculin-positives the notification rate in Scotland (which has few immigrants) (Table V) is similar to that in England and Wales (excluding immigrants) (Table VI) at age 15–19 years, but higher at age 20–24 years. In the BCG-vaccinated and tuberculin-negative groups the rates in Scotland are two or three times as great as in England and Wales (excluding immigrants). The pattern suggests that the infection risk is higher in Scotland than in England and Wales, and that it is at the level it was in England and Wales five to ten years earlier.

Notification rates in life-time residents of England and Wales in 1973 and 1978

The notification rates in Table VI are used as the basis for this discussion. The rates for the 15–19 age group in 1973, and hence the protective effectiveness, differ from those in the published report of the earlier study (British Thoracic and Tuberculosis Association 1975) because (*a*) immigrants have been excluded from both cases and populations and (*b*) allowance has been made in the population estimates for more recent information and for individuals vaccinated or found tuberculin-positive before age 13 years.

For those who are unvaccinated and *tuberculin-positive* at about age 13 years the notification rate at age 15–19 years in 1978 is 14.1 per 100 000, 20% lower than the rate of 17.7 per 100 000 in the same age group in 1973. This suggests that the general level of infection rate plays some part in influencing the notification rate in tuberculin-positives. The rate in the 20–24 age group in 1978 is substantially lower than in the

15–19 age group in either year, confirming the fall in rate at longer intervals from the positive test.

For those *tuberculin-negative* at about age 13 years the notification rate at age 15–19 years in 1978 is 10.5 per 100 000, 50% lower than the rate of 21.1 per 100 000 in the same age group in 1973. This decline is the same as the decline in infection risk that has been suggested from a tuberculin survey. In the 20–24 age group the rate of 17.4 per 100 000 in 1978 is below the rate of 21.1 per 100 000 recorded for the same cohort when aged 15–19 years in 1973.

For those *vaccinated with BCG* at about age 13 years the notification rate at age 15–19 years is 2.6 per 100 000 in 1978 and 2.5 per 100 000 in 1973. This negligible change in rate suggests either that there has been no decline in infection risk or that there is some other reason for the absence of a decline in this group. At age 20–24 years the rate of 4.2 per 100 000 in vaccinated subjects in 1978 is greater than the rate of 2.5 per 100 000 in the same cohort when aged 15–19 years in 1973.

Thus, the pattern in BCG-vaccinated subjects aged 15–19 years, in whom there has been no decline in notification rate, is quite different from that in tuberculin-negative subjects aged 15–19 years, in whom the rate has declined by 50% between 1973 and 1978. The methods adopted in the two studies were identical and the percentage response was similar. It is difficult to see how the difference in trends could be due to any differences in study procedures.

The notification rate in tuberculin-negatives has been assessed in the same way for each study, and they are not subject to any other procedure which could affect their rates, so that it is difficult to regard the decline as an artefact; the decline is unlikely to have arisen by chance ($P < 0.001$).

The absence of a similar decline in the BCG-vaccinated group could be due to changes in vaccination and related procedures in 1972–6 as compared with 1967–71. In many areas the Tine test has been introduced in recent years instead of the Heaf test. However, the recent British Thoracic Association study of the Tine test in comparison with the Mantoux test (Lunn & Johnson 1978) has cast doubt on the reliability of the Tine test in identifying those infected and its consistency in different hands. Further, from about 1972 there was a change in vaccination policy in many areas, children with Grade I reactions to the Heaf test now being vaccinated. The extent of these changes is unknown, but their effects will presumably have been similar. Both result in the transfer of a proportion of those with weak positive reactions from the tuberculin-positive to the vaccinated group. Those with weak positive reactions probably have some natural protection against the development of tuberculosis, and the expected incidence of tuberculosis among them, if they are not vaccinated, is low. The benefits of vaccination in this group are probably also small. The nett result of transferring even quite a large proportion of weak positive reactors to the vaccinated group would be a slight increase in rate in the tuberculin-positive group and no change or a slight increase in the BCG-vaccinated group. These two changes cannot resolve the anomaly.

The average viable bacterial count in the batches of BCG vaccine issued for use in Great Britain was increased in 1975, but this would scarcely lead to a reduction in efficacy of the vaccine.

There has, however, been increased use of jet injection since 1973, and perhaps also an increase in vaccination by multiple puncture techniques. The extent of these changes is also not known, but may well be substantial. Jet injection instruments show considerable technical variations (British Thoracic and Tuberculosis Association 1971*a*) and may be used by inadequately trained personnel. Multiple-puncture techniques do not give such satisfactory post-vaccination tuberculin sensitivity as do syringe and needle (British Thoracic and Tuberculosis Association 1971*b*). If a proportion of those classified as vaccinated have remained unprotected due to inadequacies of vaccination technique this could have obscured the effect of a decline in infection risk between 1973 and 1978.

Comparison with results of controlled trial started in 1950–52

The results presented have shown that the effectiveness of the schools BCG vaccination scheme in preventing notifications of tuberculosis in the calendar years 1973 and 1978 is between 69% and 88%. These results are very similar to those obtained in the Medical Research Council's controlled trial of BCG vaccination of slightly older school children in 1950–52. The protective effectiveness in that trial was 77% over a 20-year period, though little or no effect was shown in the last five years (Hart & Sutherland 1977).

The similarity of the protective effectiveness in that controlled trial and in routine use in the present study is of interest especially because of the considerable differences recorded in tuberculosis rates. In the first five years of the trial the rates in the tuberculin-negative and BCG-vaccinated groups were 250 and 40 per 100 000 respectively, and these may reasonably be compared with the rates of 10.5 and 2.6 per 100 000 in the 15–19 age group for life-time residents of England and Wales in 1978 shown in the present study. In the second five years of the Medical Research Council trial the rates in these groups were 106 and 33 per 100 000, compared with 17.4 and 4.2 per 100 000 in the 20–24 age group in the present study.

Even in the tuberculin-positive group the rates have fallen considerably, from 149 per 100 000 in the first five years of the Medical Research Council trial to 14.1 per 100 000 at age 15–19 in 1978, and from 53 per 100 000 in the second five years of the trial to 7.6 per 100 000 at age 20–24 years in 1978.

Number of notifications prevented by BCG vaccination

This is an alternative method of expressing the results which was used in the report of the 1973 study (British Thoracic and Tuberculosis Association 1975). The estimates given below differ from those given in that report for two reasons:

1. The change in method in estimating the populations at risk, the details of which are recorded earlier in this paper. The method now adopted is regarded as giving more reliable estimates.

2. The more complete data now available for the cohort aged 15–19 years in 1973 has led to a revision of the estimates for that as well as the subsequent cohort.

The first line of Table VII shows the number of notifications that would have been prevented in 15 years following 100 000 vaccinations in 1950–52. In the first five years of that study the annual notification rate was 210 per 100 000 less in BCG vaccinated subjects than in tuberculin-negatives, in the second five years it was 73 per 100 000 less, and in the third five years it was 16 per 100 000 less, with little difference subsequently. Each of these rates was considered to operate for a five-year period, so that the total reduction in notifications from 100 000 vaccinations at that time would have been

5 (210 + 73 + 16) = 1495. This can also be expressed in the form that 67 vaccinations at that time would have prevented one notification in the next 15 years.

The results from the present report are expressed in similar form in the lower part of Table VII, but some additional assumptions are made. For the cohort vaccinated in 1967–71 reasonably direct measurements of the notifications prevented are available for 1973 and 1978, representing the notifications prevented at ages 15–19 and 20–24 years. At age 15–19 years the reduction is 21.1 − 2.5 = 18.6 per 100 000 per year falling to 17.4 − 4.2 = 13.2 per 100 000 at age 20–24 years in 1978. It is then assumed that the fall in notifications prevented between age 20–24 years and age 25–29 years is in the same proportion as between age 15–19 years and age 20–24 years. This gives 5(18.6 + 13.2 + 9.4) = 206 notifications prevented in 15 years following 100 000 vaccinations in 1967–71.

Table VII. Estimates of notifications prevented in 15 years following 100 000 vaccinations in England and Wales

Period of vaccination	*Notifications prevented*	*Vaccinations to prevent one notification*
1950–52 (MRC)	1495	67
1967–71	206	500
1972–6	88	1150
1977–81	44	2300
1982–6	22	4600

For the next cohort only the reduction in notifications at age 15–19 years in 1978 is directly available (7.9). It is assumed that the reduction in the two older five-year age groups are in the same proportion as for the preceding cohort, to give a figure of 5(7.9 + 5.6 + 4.0) = 88 notifications prevented in 15 years after 100 000 vaccinations in 1971–6. The remaining two lines of Table VII are based on the assumption that the infection risk and number of cases prevented continue to fall by about 50% in five years and lead to a figure of 44 cases prevented in 15 years by each 100 000 vaccinations in the period 1977–81.

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Reprints can be obtained from the Administrative Secretary, British Thoracic Association, 30 Britten Street, London SW3 6NN.

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A STUDY OF INFECTIVE AND OTHER FACTORS IN EXACERBATIONS OF CHRONIC BRONCHITIS

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INTRODUCTION

In a study of causative factors in exacerbations of chronic bronchitis carried out in 1965–8 in Edinburgh by Fisher et al. (1969), evidence of viral or bacterial infection was found in only 44% of the exacerbations investigated. Subsequent improvements in the techniques for identifying respiratory viruses made it seem desirable to carry out a further study, using the same general methods and, in particular, the same definition of an exacerbation. In order to investigate possible geographical differences, two groups of men were followed up in the present study, one in Edinburgh and one in London. Great care was taken to standardize the methods used in each centre.

Materials and Methods

Thirty-eight men were studied, 18 in Edinburgh and 20 in London. All had 'chronic or recurrent mucopurulent obstructive bronchitis', as defined by the MRC (1965). Patients with bronchiectasis, arrested pulmonary tuberculosis or other disease causing widespread lung damage were excluded from the study. No patient admitted to the study was taking long-term prophylactic antibiotics.

Patients were excluded if their forced expiratory volume in one second (FEV_1) increased by more than 30% within 20 minutes of two inhalations of salbutamol aerosol. The mean FEV_1 of the 38 patients on recruitment was 1.40 litres (SD 0.59 litre). After salbutamol, FEV_1 increased by less than 10% in 29 patients and by 11–29% in eight others. In the remaining patient FEV_1 increased by 33% but, because the absolute increase was only 0.20 litre from a resting value of 0.60 litre and also because he was a typical bronchitic in all other respects, he was retained in the study. Of the 38 patients 20 either had previously received a trial of prednisolone (at least 20 mg a day for two weeks) or were given such a trial on the completion of the study; in none was there any improvement in daily measurements of peak expiratory flow (PEF).

At the beginning of the study 29 (76%) of the 38 patients were aged 60–69 years, the other nine being aged 44–54 years. 26 patients were currently smoking, of whom three stopped during the study. Nine (24%) of the patients' households contained children.

The study covered the period January 1975 to April 1977 and included two complete winters. Four patients were withdrawn; one because of the development of carcinoma of the bronchus and three because they proved uncooperative. One patient moved to another district and was lost to follow-up. Two patients died during the survey (one from carcinoma of the oesophagus and one from myocardial infarction). Data obtained from these seven patients during the periods in which they were followed up have been included in the analysis.

A detailed history was taken to ensure that patients fulfilled the criteria of the MRC definition of chronic or recurrent mucopurulent obstructive bronchitis and that they had no other respiratory condition which would have excluded them from the study.

Patients attended every four weeks for routine review. Enquiry was made about any change in their symptoms or smoking habits during the previous four weeks. They were asked to notify the coordinators as soon as they began a head cold or throat infection or if they considered that their habitual symptoms of expectoration or breathlessness had increased in severity. They were seen as soon as possible after the receipt of this notification, and were questioned about the following symptoms: coryza, sore throat, hoarseness, increased cough, increased wheeze, increased sputum and a change in colour of sputum to green or yellow. An exacerbation was deemed to have occurred if a patient reported either *an increase of cough or wheeze or a change in sputum colour, plus at least one other item on the above list*, or *an increase in sputum volume* (whether or not it was accompanied by anything else on this list).

At every routine attendance the following specimens were obtained: (*a*) an early morning specimen of sputum; (*b*) nasal and pharyngeal swabs; and (*c*) a specimen of blood. In exacerbations the same specimens were obtained and an additional blood specimen was taken two to three weeks later. Nasal and pharyngeal swabs were placed in a bijou bottle containing virus transport medium (Hanks' BSS with 0.2% bovine albumen, ampicillin 200 μg/ml, and penicillin 150 international units/ml) and were kept at 4°C until delivered to the laboratory. Sputum specimens were collected in sterile containers and were stored at room temperature. Whenever possible, specimens were delivered to the laboratory on the same day, but occasionally they had to be stored overnight. The laboratory methods used in Edinburgh and London were identical and are described below.

Infection by viruses and other non-bacterial agents

Isolation. Before inoculating specimens into cell cultures, the bottles were shaken to liberate cells from the swabs into the medium. Sputum was homogenized in Hanks' BSS with glass beads. Inoculation of the suspensions was made into the following cell cultures: secondary rhesus monkey kidney, diploid human embryo lung fibroblasts (MRC5) and human embryo kidney cells, all of which were maintained on a roller drum at 33°C. Inoculation was also made into cultures of HEp2 cells which were maintained stationary at 36°C. All cultures were observed for three weeks and, if there was no evidence of the presence of virus, discarded. If, however, the cells had degenerated a second passage in similar cells was made for at least a further week. Monkey kidney cultures were tested twice weekly for haemadsorption, using guinea pig erythrocytes. The diagnostic sera used for most identification purposes were supplied by the Standards Laboratory for Serological Reagents, Central Public Health Laboratory, Colindale. Rhinoviruses were identified by their cytopathic effect in MRC5 cell cultures and by their lability to acid. A selective diphasic medium, similar to that described by Chanock et al. (1967), was used for the isolation of *Mycoplasma pneumoniae.*

Serology. Complement fixation (CF) tests, were carried out against the following agents: influenza viruses (types A and B), Sendai virus, adenoviruses, respiratory syncytial virus, chlamydia group B, *Coxiella burneti* and *M. pneumoniae*. Sera were screened at a dilution of 1:16. If positive, the patient's previous specimen was titrated in parallel. A fourfold or greater rise in titre was regarded as diagnostic of recent infection. A haemagglutination inhibition (HAI) test was used to identify infection by coronavirus strain OC43, the antigen being propagated in suckling mouse brain.

Bacterial infection

Sputum culture. The sample of sputum was homogenized by shaking with sterile distilled water and glass beads and inoculated on (*a*) blood agar, (*b*) heated blood agar (with bacitracin 10 units/ml), and (*c*) MacConkey agar. All plates were incubated in 10% carbon dioxide for 18 hours. Homogenized sputum was inoculated into adult mice by the intraperitoneal route. The sensitivity of organisms to ampicillin, tetracycline, benzyl penicillin and cotrimoxazole was assessed by Stokes' method, using the Oxford *Staphylococcus* as control organism.

Immunology. During the early part of the study, paired specimens of sputum and serum were obtained from certain patients both at routine attendances and in exacerbations and were sent to Middlesex Hospital Department of Immunology, where they were examined for antibodies of different classes to components of *Haemophilus influenzae* by radio-immunoassay (Bull & Smith 1980).

Sputum cytology

Before homogenization of the sputum sample, one film was made from its most purulent part and stained by Gram's technique. Two films were prepared and stained by the chromotrope 2R method. Microscopic purulence was graded as follows: M = no pus cells present; Pc+ = small number of pus cells (1 to 9 cells per oil immersion (× 100) field); Pc++ = moderate number of pus cells (10–19 cells/field); and Pc+++ = numerous pus cells (20 or more cells/field). Eosinophil polymorphonuclear leucocytes were counted and expressed as a percentage of the total number of leucocytes per high power field.

Tests of ventilatory function

Measurements of forced expiratory volume in 1 second (FEV_1), forced vital capacity (FVC) and peak expiratory flow rate (PEF) were made at every routine attendance.

Meteorological data

Data relating to temperature, wind velocity and direction, and levels of smoke and sulphur dioxide were obtained from Edinburgh Airport and Kew Observatory.

RESULTS

No differences emerged between Edinburgh and London in the characteristics of the patients studied, nor in the meteorological data obtained throughout the study. Therefore the findings from the two centres have been combined.

The study lasted 28 months. The total period of observation was 695 patient-months. The duration of observation of individual patients ranged between two and 27 months: in 53% of patients it was more than 20 months, and in 79% more than 12 months.

Patients were seen for monthly follow-up on 636 occasions. Exacerbations were reported on 116 occasions, 79 of which were notified within three days of the onset of symptoms. On 37 other occasions when patients attended for routine follow-up they reported that since their last attendance they had had symptoms which fulfilled our criteria of an exacerbation. These 'missed' exacerbations were not notified for a variety of reasons, such as absence on holiday, the imminence of their next routine attendance or the wish to avoid troubling their doctors (although they were reminded at every routine attendance to report any new symptoms at once).

Distribution of exacerbations

The distribution of all the 116 notified and missed exacerbations is shown in Table I. The larger number of exacerbations in London (70) than in Edinburgh (46) is largely accounted for by four men in London who had seven or eight exacerbations. Five men had no exacerbations during the study.

The majority (75%) of exacerbations occurred between October and March. Daily climatic data, including air temperature, wind velocity and direction and levels of

Table I. The distribution of all exacerbations (79 investigated and 37 'missed') which occurred in the course of the study

Exacerbations per patient	*No. of patients*			*Total No. of exacerbations*
	Edinburgh	London	Total	
0	2	3	5	0
1	2	1	3	3
2	6	3	9	18
3	5	5	10	30
4	0	2	2	8
5	2	2	4	20
6	0	0	0	0
7	1	2	3	21
8	0	2	2	16
Total	18	20	38	116

smoke and SO_2 were plotted but no correlation could be discerned between changes in any of them and the incidence of exacerbations.

Examination of the serial measurements of FEV_1 disclosed no instance in which a persistent fall occurred in relationship to an exacerbation.

Infection by viruses and other non-bacterial agents (Table II)

Specimens were obtained on the day of notification in all of the 79 notified exacerbations. Of the 37 'missed' exacerbations, seven had begun less than eight days previously and for the purpose of analysing the virological findings it was decided to add these seven to the 79 notified exacerbations, making a total of 86. The 30 remaining 'missed' exacerbations were added to the 599 routine attendances, making a total of 629.

Infection by respiratory viruses or other non-bacterial agents was identified in 17 (20%) of exacerbations and at 36 (6%) of routine attendances (Table II), the difference between these identification rates being highly significant ($P < 0.001$). Of the 30 'missed' exacerbations included with the routine attendances (because they had begun eight or more days before being investigated), there was serological evidence of recent infection in seven (23%). None of the rises in titre against influenza A and B viruses were a consequence of immunization. In some of the cases when viruses were isolated at routine attendances, patients currently had symptoms of upper respiratory illness but in the majority infection was subclinical.

Rhinoviruses were by far the most commonly isolated agents in exacerbations, accounting for more than half of all viruses identified. There was a highly significant difference ($P < 0.001$) between their isolation rates in exacerbations and at routine attendances. In contrast, no significant difference was found between exacerbations and routine attendances in the identification rates of either influenza A and B viruses or parainfluenza viruses.

Purulence of sputum

There was Grade 2 or 3 purulence in over half the specimens of sputum obtained in exacerbations and routine attendances. However, a significant difference ($P < 0.005$) was

Table II. Respiratory viruses and other non-bacterial agents identified at exacerbations and routine attendances

	Exacerbations		*Routine attendances*	
	Isolations	Serological	Isolations	Serological
Influenza A virus	2	1	2	4
Influenza B virus	0	1	0	2
Influenza A + B virus	0	0	0	1
Parainfluenza virus 1 (Sendai)	1	0	4	1
Parainfluenza virus 3*	0	—	3	—
Rhinoviruses*	11	—	5	—
Echoviruses*	0	—	2	—
Coxsackie A virus*	0	—	2	—
Respiratory syncytial virus	0	0	0	2
Adenoviruses	0	0	2	1
Coronavirus OC43†	—	1	—	2
Chlamydia psittaci†	—	0	—	1
Coxiella burneti†	—	0	—	1
Mycoplasma pneumoniae	0	0	0	1
	14	3	20	16
Total identifications	17		36	
Total number of episodes investigated	86		629	
Percentage in which viral infection was identified	20%		6%	

*Specific serological tests not undertaken. Complement fixative tests not applicable.

†These agents cannot be isolated in cell cuture under conventional laboratory conditions.

found between the purulence rate in exacerbations (73%) and that in routine attendances (53%). Although the isolation rate was higher in the most purulent sputum from exacerbations no statistically significant correlation was detected between the grades of purulence and the isolation rates either during exacerbations or at routine attendances.

Bacterial infection: sputum culture (Fig. 1; Table III)

Because there is general agreement that *H. influenzae* and *Streptococcus pneumoniae* are the most important pathogenic bacteria found in chronic bronchitis (May 1972) and because very few isolations were made of any other bacteria only these two bacteria have been considered in analysis.

The bacteriological findings in all 37 'missed' exacerbations have been included with those of routine attendances, since organisms identified at a subsequent routine attendance could not confidently be attributed to the preceding exacerbation.

In notified exacerbations *H. influenzae* or *S. pneumoniae* was identified in 23 (30%) of 77 exacerbations and in 135 (22%) of 628 routine attendances, there being no significant difference between these isolation rates. In only four exacerbations in which a virus was isolated was there evidence of simultaneous bacterial infection.

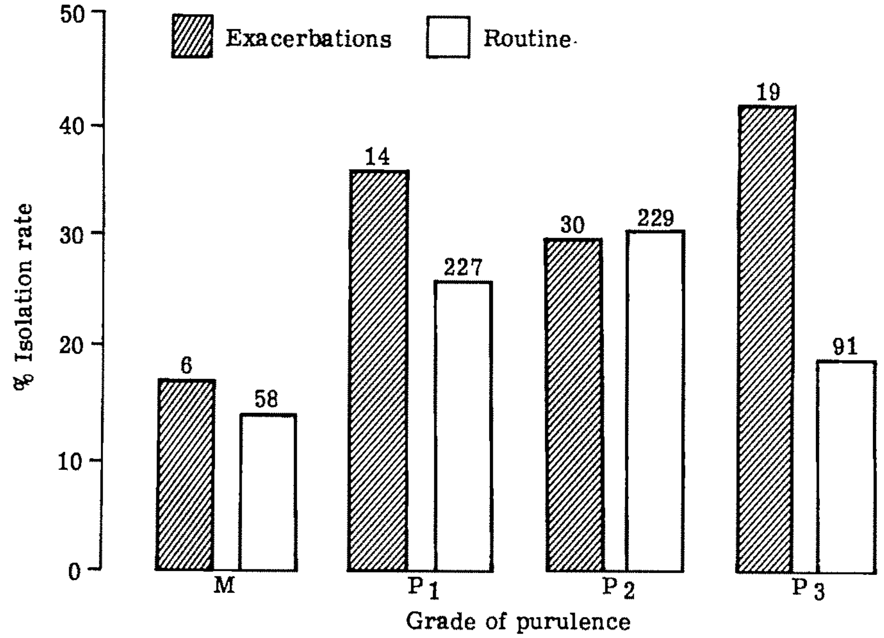

Fig. 1. Isolation rates of pathogenic bacteria in sputum, according to grade of purulence, in exacerbations and at routine attendances. The figures above each column denote the total number of specimens examined

Table III. 'Pathogenic' bacteria isolated from sputum in investigated exacerbations and at routine follow-up

Bacterial	*Exacerbations* ($n=77$)	*Routine specimens* ($n=628$)
H. influenzae	9 (12%)	69 (11%)
S. pneumoniae	11 (14%)	48 (8%)
H. influenzae *S. pneumoniae*	2 (3%)	14 (2%)
Staph. pyogenes	1 (1%)	4 (1%)
Total	23 (30%)	135 (22%)

The difference in isolation rates between exacerbations and routine specimens was not significant.

Bacterial infection: immunology

Preliminary analysis showed that antibodies in serum to the H_1 antigen of *H. influenzae* (Burns & May 1967) were present in high titre in the majority of patients. In a few patients sharp rises in titre accompanied exacerbations. The findings will be reported in detail elsewhere together with those from sputum.

Sputum and blood eosinophilia

Of the 38 patients, 33 (87%) had a sputum eosinophilia greater than 10% on at least one occasion. Eosinophil counts were generally higher at routine attendances than in exacerbations: thus, at routine attendances 22 (58%) of the patients had a greater than 50% eosinophilia on at least one occasion, whereas in exacerbations eosinophilia of this degree was found in only six (21%) of the 29 men who had exacerbations during the study. There was no correlation between sputum eosinophilia and viral infection. Most of the patients who had the highest eosinophil counts had negative skin tests against common allergens.

There was no obvious consistency in the pattern of sputum eosinophilia. Few patients had a persistently elevated eosinophilia and in most cases high counts were found at two or three consecutive routine attendances to be followed by several months during which no, or few, eosinophils were present.

Absolute eosinophil counts in the blood did not reflect the sputum eosinophilia. In only four patients did the former exceed 500×10^9 cells/litre and in the majority it was less than 250×10^9 cells/litre.

Skin prick tests

These were performed in 31 patients, using solutions of housedust, housedust mite, grass pollens, animal hairs and dander, *Aspergillus fumigatus* and control. One or more positive reactions were obtained in six (19%) of those tested. Three of the patients with positive reactions frequently had high eosinophil counts in the sputum whereas the other three had very low counts throughout the study.

Mediators of hypersensitivity reactions in sputum

Examination of sputum from the Edinburgh patients disclosed variable levels of histamine, SRS-A and IgE: these findings have been reported elsewhere (Turnbull et al. 1977; 1978*b*).

DISCUSSION

The principal aim of this study was to clarify the role of infection in exacerbations of chronic bronchitis. It was disappointing, therefore, that the identification rates of viruses and bacteria in exacerbations were lower than we had hoped. Nevertheless, the isolation rate of viruses in this study (20%) was an improvement on that obtained in the previous study (14%) carried out in Edinburgh in 1965–8 (Fisher et al. 1969).

The two most notable findings to emerge from this study were the association between rhinovirus infection and exacerbations and the frequency of high eosinophil counts in sputum during remissions in contrast to the generally low counts found in exacerbations. Comparisons of the findings of the present study with those of the earlier study in Edinburgh carried out ten years previously are also of some interest.

The severity of chronic bronchitis in the men selected for the present study was similar to and possibly greater than that of the men studied in 1965–8, but the mean age was higher with 76% older than 60 years. In the previous study only 44% of the men were aged more than 60 years and over half of them had participated in a trial of 'early' chronic bronchitis (Medical Research Council 1966) a few years beforehand.

A striking difference between the two studies was the frequency with which purulent sputum (grades 2 and 3) was found, particularly at routine attendances (Fig. 1). In the earlier study only 17% of routine specimens were purulent, whereas 53% were purulent in the present study ($P < 0.001$). In exacerbations 52% of specimens were purulent in the earlier study and 73% in the present study ($P < 0.02$). These differences may have resulted from long-term antibiotic prophylaxis which was taken throughout the winter by over half of the patients in 1965–8 but by none in the present study.

Another difference between the studies may also be attributable to long-term antibiotic therapy. In 1965–8 the isolation rate of pathogenic bacteria at routine attendances was only 9%, compared with 22% in the present study. However, while antibiotic prophylaxis may have suppressed persistent infection, it would appear to have been far less effective in preventing acute bacterial infection at exacerbations, for the isolation rate was 39% in the previous study. In the present study, in which long-term chemotherapy was not used, the isolation rate in exacerbations was 30%. It is difficult to explain why this isolation rate was not higher and was inconsistent with the high rate of sputum purulence.

The identification rate of viruses and other non-bacterial agents achieved in the present study is similar to that obtained in most other similar studies. The most important finding was the relatively large number of rhinoviruses isolated and it is possible that even more might have been isolated if WI 38 cell culture, which is particularly sensitive to rhinoviruses, had not ceased to be available shortly before the study began.

An association between infection by rhinoviruses and acute episodes of bronchitis and asthma has been reported by other workers, both in adults (Eadie et al. 1966; Stenhouse 1967; Lambert & Stern 1972; Gregg 1975; Minor et al. 1976) and in children (Gregg 1970; Minor et al. 1974*a*, *c*; Mitchell et al. 1978; Horn et al. 1979).

The mechanisms whereby respiratory virus infection provokes bronchitis and/or wheeze have been discussed by Gregg (1975) and Horn et al. (1979), who postulated that one essential factor must be some defect in the defences of the lower respiratory tract against viral infection. The highly significant difference between the isolation rates of rhinoviruses in exacerbations and routine attendances suggests that in patients with chronic bronchitis infection by rhinoviruses is seldom confined to the upper respiratory tract and that these agents have a particular tendency to provoke an exacerbation. It seems probable that their importance is due to their large number of antigenically distinct serotypes (Roebuck 1976) and the absence of cross-immunity between them (Minor et al. 1974*b*; Horn et al. 1979). Thus, if a bronchitic is infected by a rhinovirus he would be unlikely to escape an exacerbation unless he was immune as a result of a recent infection with that particular serotype.

Lambert and Stern (1972) drew attention to the importance of family structure as a determinant of the risk of infection in patients with chronic chest disease. In both the previous and the present study a quarter of the patients had children in their households. In the study by Eadie et al. (1966), in which they demonstrated rhinovirus infection in 23% of exacerbations in chronic bronchitics, a higher proportion (39%) of households contained children.

Influenza is well recognized to be a danger to chronic bronchitics and it was surprising that infection by influenza A and B viruses seldom occurred in either the Edinburgh or London patients, despite epidemics during two of the three winters of the present study. Whereas in the previous study these viruses accounted for almost half of all those identified in exacerbations, they were seldom associated with exacerbations in the present study, despite the fact that only four patients received influenza vaccine during the study.

Although sputum eosinophilia is commonly believed to be a distinguishing feature between chronic obstructive bronchitis and asthma, other workers have also found sputum eosinophilia in patients with chronic respiratory disease who did not apparently have asthma. In 30 patients, described as having emphysema, Cole et al. (1959) examined sputum daily for 28 consecutive weeks. In half the patients they observed periodic 'showers' of eosinophils with counts between 40% and 100% which lasted a few days and occurred every few weeks. Their observations were similar to our own, as was their failure to find any correlation between eosinophilia and changes in symptoms or meteorological conditions. Miller (1963) studied 1174 working men and found that 39% of them had sputum eosinophilia at some time. O'Connell et al. (1978) studied 115 men with chronic bronchitis, asthma or both to determine the diagnostic, therapeutic and prognostic implications of sputum eosinophilia. They, too, found no correlation with positive skin tests. They concluded that sputum eosinophilia was of little value for distinguishing between chronic bronchitis and asthma and they postulated the existence of local allergic and non-allergic factors which might be responsible for eosinophil release in the bronchi.

In the present study patients were carefully screened to exclude any with asthma and were given a trial of steroids which showed that none had latent reversibility of airflow obstruction. Our finding of the high frequency of sputum eosinophilia led to subsidiary studies by Turnbull et al. (1977, 1978*a*, *b*). They demonstrated that IgE and mediators of type 1 hypersensitivity were frequently present in the sputum of chronic bronchitics and they also showed a significant inverse relationship between the concentration of these mediators and changes in airflow obstruction, measured by serial PEF. Our findings and theirs suggest that hypersensitivity reactions may play a part in at least some exacerbations of chronic bronchitis. This possibility needs to be explored further.

The rate of exacerbations per patient-month of observation in the recent study was not significantly different from that in 1965–8. In both there was a clear tendency for exacerbations to occur during the winter months, but it was impossible to discern any relationship between their incidence and changes in various meteorological indices including atmospheric pollution.

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machinery. Zaditen may poten
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corticosteroids, should be grad
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drugs.
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Amoxil's ability to penetrate bronchial secretions whether purulent or mucoid, may explain why it has been shown to be more effective than cotrimoxazole or ampicillin in preventing relapse in bronchitis.[1] Amoxil also achieves significantly higher levels than ampicillin in both the maxillary sinus mucosa[2] and middle ear fluid.[3]

Powerful Spectrum

Amoxil's broad spectrum of activity extends across the Gram-positive and Gram-negative pathogens responsible for the vast majority of respiratory and urinary infections. In particular, Amoxil is notably active against H. influenzae, a predominating pathogen in lower respiratory infection and otitis media,[4] and against E. coli, the organism largely responsible for simple urinary infection in general practice.

Penicillin Safety

As a penicillin, Amoxil is well tolerated and suitable for most patients, including the elderly and pregnant women. Penicillin hypersensitivity is the only contra-indication.

Prescribing Simplicity

The absorption of Amoxil is virtually unaffected by the presence of food[5] which adds to the convenience of its t.d.s dosage. And for urinary infections in adults, Amoxil Twin Pack, the complete two dose course of treatment, is simplicity itself.

Amoxil

amoxycillin

Proves Successful

Indications: Cystitis, urethritis, pyelonephritis. Bacteriuria in pregnancy. Gonorrhoea. Skin and soft tissue infections. Acute and chronic bronchitis. Upper respiratory tract infections. Otitis Media. Pneumonia. **Presentations:** Amoxil capsules: 250mg and 500mg; PL 0038/0103/5. Amoxil syrup: 125mg and syrup forte 250mg per 5ml; PL 0038/0108/9. Amoxil paediatric suspension: 125mg per 1.25ml; PL 0038/0107. Amoxil 3g sachet: 3g per 50ml; PL 0038/0238. Amoxil vials for injection: 250mg, 500mg and 1g; PL 0038/0221/2/5. The amoxycillin content per dose unit is present as the trihydrate in Amoxil oral preparations and as the sodium salt in Amoxil injections. Average daily cost for adults (250mg capsules t.d.s.) is 37p and for children (125mg syrup t.d.s.) is 24p at time of printing. **Dosage: Adult Dosage** Oral: 250mg three times a day. In severe infections doses should be doubled. In simple, acute urinary tract infection in adults two 3g doses amoxycillin (Twin Pack) with 10-12 hours between the doses. Injectable: 500mg IM 8 hourly (or more frequently if necessary) in moderate infections. 1g IV 6 hourly in severe infections. **Childrens Dosage (up to 10 years of age)** Oral: 125mg three times a day. In severe infections doses should be doubled. Injectable: 50-100mg/kg bodyweight per day, in divided doses. **Contra-indications:** Amoxil is a penicillin and should not be given to penicillin hypersensitive patients. **Side-effects:** Side-effects, as with other penicillins, are usually of a mild and transitory nature: they may include diarrhoea, indigestion or occasionally rash, either urticarial or erythematous. The urticarial rash suggests penicillin hypersensitivity, and the erythematous type rash may arise if Amoxil is administered to patients with glandular fever. In either case treatment should be discontinued. Since Amoxil is a penicillin, problems of overdosage are unlikely to be encountered. Further information on Amoxil (regd.) amoxycillin is available from:
Bencard, Great West Road, Brentford, Middlesex. Tel: 01-560 5151.

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CILIARY MOTILITY IN THE 'IMMOTILE CILIA SYNDROME'

First Results of Microphoto-oscillographic Studies

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Summary

Using a microphoto-oscillographic technique the authors studied ciliary beating of nasal epithelial cells from 11 patients with the 'immotile cilia syndrome' (Kartagener's syndrome) and from normal controls. Ciliary motility was found in all patients, except one. Although the patients had a significantly reduced number of cells with motile cilia, one-third of all ciliated cells showed motility. The beating frequency was normal, but the motility pattern was highly abnormal, with a predominance of asynchronous motility in the patients. These results suggest that the lack of dynein arms in cilia in these patients only is partial and that direct observation of ciliated cells, obtained by gentle scraping on the nasal mucosa, may be a suitable screening test for early diagnosis of this syndrome.

INTRODUCTION

A few years ago it was shown that four infertile men with immotile spermatozoa lacked the ATP-ase containing dynein arms in the sperm tail (Pedersen 1974; Afzelius et al. 1975; Pedersen & Rebbe 1975). As a result of this finding it was demonstrated that the dynein arms were also absent in respiratory tract cilia from patients with Kartagener's syndrome (Afzelius 1976; Pedersen & Mygind 1976), a triad consisting of situs inversus viscerum, chronic rhinosinusitis, and chronic bronchitis with bronchiectases (Kartagener 1933). As these patients demonstrated no mucociliary transport in the nose (Pedersen & Mygind 1976) or bronchi (Camner et al. 1975), it was logical to assume that their cilia were immotile, although this had not directly been observed. Eliasson et al. (1977) proposed the name 'immotile cilia syndrome' for male sterility and chronic infections of the upper and lower airways, irrespective of the presence of situs inversus, which these authors emphasized was present in only half of the patients. Consequently, a diagnosis could not be based merely on case history and radiographic examination.

Early diagnosis is of importance for the prognosis of another chronic airway disease, cystic fibrosis (Warwick & Pogue 1968), because daily physiotherapy, frequent bacteriological examination and active antibiotic therapy can thereby commence. An early diagnosis of the 'immotile cilia syndrome', resulting in active therapy, could probably prevent the development of bronchiectases and damage to lung tissue.

For the past two years, the authors have studied the ciliary beating pattern in patients with suspected 'immotile cilia syndrome' for two reasons: first, to understand better the defect of the disease and with that the motility mechanism of cilia, and second, and most important, to develop a diagnostic test, which is not prohibitively time-consuming, and which can be used with infants. The findings from the first 11 patients are here reported.

Material and Methods

All patients examined had had daily nasal discharge and productive cough since infancy. All but three had situs inversus of the heart or gastrointestinal tract (Table I). A constant finding by rhinoscopy was accumulation of mucopurulent secretions in the nose, especially under the inferior turbinate. Typically, these patients could provide a productive cough and nose-blowing on request. At repeated examinations no mucociliary transport could be detected in the nose by the saccharine-dye test (Andersen et al. 1974).

Table I. Characteristics of 11 patients with 'immotile cilia syndrome'

Patient	*Sex*	*Age* (years)	*Situs inversus*	*Bronchiectases*
1	F	11	No	Confirmed
2	F	18	Heart	Suspected
3	M	15	Gastrointestinal tract	Confirmed
4	F	31	Heart and gastrointestinal tract	Confirmed
5	M	9	No	No
6	M	5	Heart and gastrointestinal tract	Suspected
7	F	30	No	Suspected
8	F	3	Heart and gastrointestinal tract	No
9	M	½	Heart and gastrointestinal tract	Not suspected
10	M	35	Heart and gastrointestinal tract	Not suspected
11	F	26	Heart and gastrointestinal tract	Not suspected

Epithelial cells for electron microscopy were at first obtained from nasal biopsies, but later from gentle scraping on the nasal mucosa with a sharp spoon (diameter 2 mm). This painless procedure can be performed without bleeding even in newborn infants. Specimens were fixed in glutaraldehyde and processed as described elsewhere (Pedersen 1974; Pedersen & Mygind 1976). Electron microscopy was performed in two patients without situs inversus and in three patients with complete Kartagener's syndrome. The photomicrographs showed total or partial absence of dynein arms and, in some cilia, an abnormal arrangement of microtubules (Fig. 1).

With the sharp spoon, a sample of about 1000 living cells was obtained for direct microscopic observation from all 11 patients, from 12 normal subjects and from 13 patients with chronic and recurrent airway infections, not started in infancy. The specimen was immediately placed in Ringer's solution in a chamber (diameter 20 mm; height 70 μm) and the number of cells with motile cilia per 100 ciliated cells was counted in an anoptral contrast microscope, equipped with a microphoto-oscillograph (Chevance & Lennon 1970). In all specimens (with one exception) the ciliary beating pattern was recorded in 20 cells, which were selected as the most actively beating cell in each of 20 microscopic fields (magnification × 320). Only separate cells lying in a monolayer were studied. After focussing on the bunch of beating cilia in a single cell, an aperture (diameter 0.63 mm) covering 2.1 μm of the cell was introduced in the light beam. The changing intensity of the light signal, caused by ciliary activity, was recorded by a photocell, connected with a writer. The frequency, amplitude and degree of asynchrony could then be read directly on a curve. A five-point scale was employed for synchrony/asynchrony (Fig. 2). This microphoto-oscillographic method is described in detail elsewhere (Pedersen 1980).

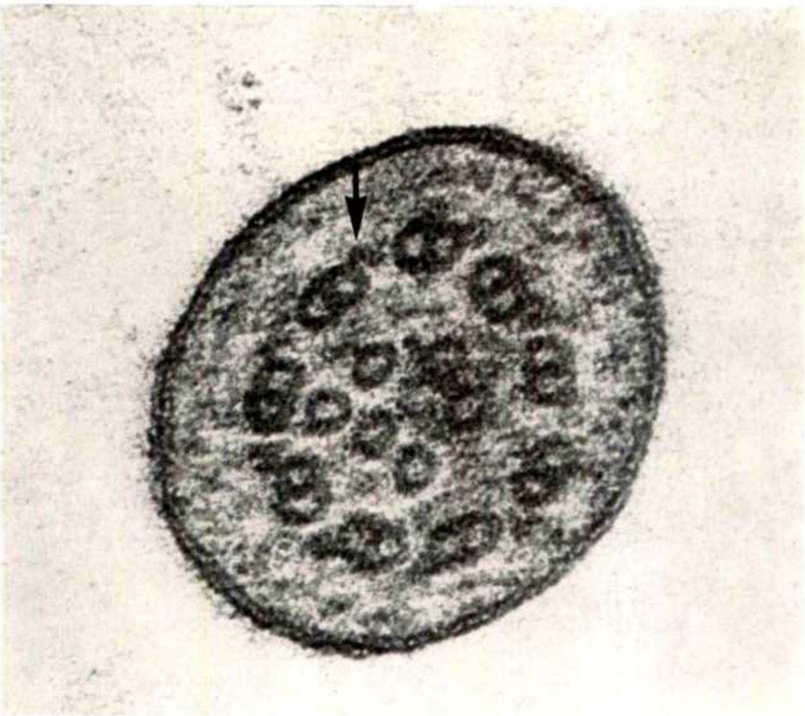

Fig. 1. Cilia from a patient with Kartagener's syndrome. Dynein arms are present on some outer microtubules (arrow); abnormal arrangement and number of central microtubules. × 122 000

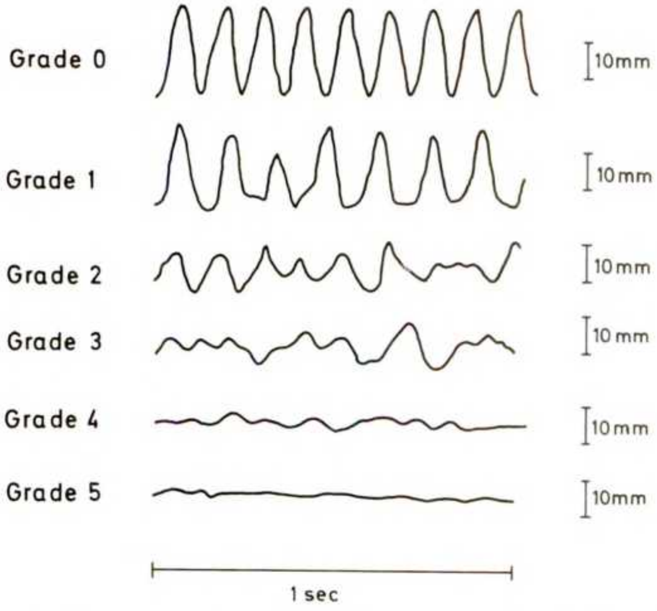

Fig. 2. Microphoto-oscillographic registration of cilia motility on single cells. Examples of different grades of asynchrony from 0 (= synchrony) to 5 (total asynchrony)

RESULTS

Ten of the 11 patients with the 'immotile cilia syndrome' had motile cilia in the nasal scraping. For the group as a whole the number of cells with motile cilia was significantly less than the normal controls ($P < 0.01$), but the variation among patients was considerable, some having a normal number of cells with motile cilia (Fig. 3). The subjects with chronic and recurrent infections had with a few exceptions a normal number of motile cells. In the 'immotile cilia syndrome' group the beating frequency was normal, while

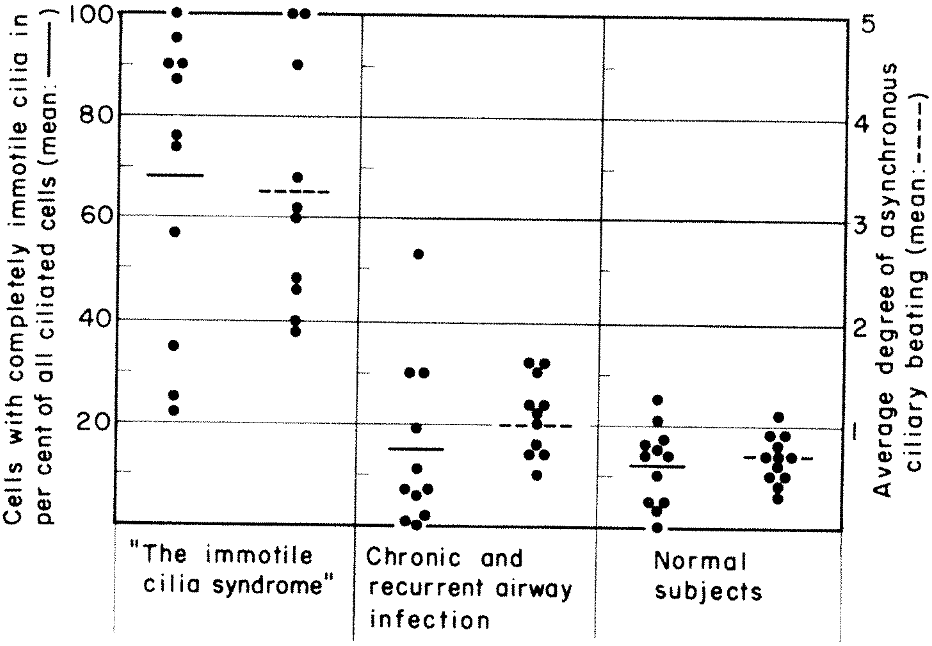

Fig. 3. Results of in vitro study of ciliated cells from the nasal mucosa. Each point represents the mean value of recordings from 100 or 20 cells (see text), from one patient. The column on the left shows percentage of all ciliated cells with completely immotile cilia. Column on the right shows the degree of asynchronous ciliary beating

Table II. Results of microphoto-oscillographic study of ciliated cells

	Normal controls ($n = 12$)	*Chronic and recurrent airway infections* ($n = 13$)	*'Immotile cilia syndrome'* ($n = 10$)
Beating frequency (average number of cycles per second) (mean ± SE)	5.5 ± 0.4	5.5 ± 0.3	5.8 ± 0.7
Beating amplitude (minimum and maximum amplitude in mm on the oscillographic curve) (mean ± SE)	6.3 ± 0.3^{a} 8.2 ± 0.4	6.0 ± 0.6^{b} 8.4 ± 0.8	2.8 ± 0.7^{c} 5.9 ± 1.1

a and *c*: $P < 0.01$; *b* and *c*: $P < 0.02$; NS for other comparisons.

the amplitude on the oscillographic curve was reduced, which may in part be due to an increased angular velocity of the individual cilia (Table II). The most marked difference was found in the coordination of the cilia in a single cell (Fig. 3). While 86% of the ciliated cells in the 'immotile cilia syndrome' patients had a highly asynchronous pattern (defined as a score of more than 2 in Fig. 1), this was only the case in 14% of the normal controls ($P < 0.01$), and in 24% of the patients with chronic and recurrent infections ($P < 0.01$ for comparison with both groups).

Comments and Conclusions

As a result of the first report of absent mucociliary transport and ultrastructural defects of cilia in Kartagener's syndrome (Camner et al. 1975; Pedersen & Mygind 1976), it was believed that the normal effective-recovery stroke of cilia in the airways was replaced by a complete stand-still, and therefore the term 'immotile cilia syndrome' was suggested and widely accepted (Fawcett 1977). Our present demonstration of motile cilia in 10 of 11 of such patients shows that this is an oversimplification. A total stand-still was characteristic of most cells in about two-thirds of the patients, while abnormal motility was characteristic in the rest; the normal stroke was replaced by unsynchronized 'trembling movements'. It is not yet known whether the distinction between subjects with predominantly immotile cilia and subjects who have mainly motile cilia with an abnormal motility pattern is reliable. Such could be suggested in relation to the finding of two ultrastructural abnormalities in these subjects: the absence of dynein arms and the abnormal arrangement of microtubules. A recent report (Sturgess et al. 1979) has shown that other ultrastructural defects could also be of significance.

On an average, every third ciliated cell from our Kartagener patients had motile cilia. Considering the high number of ciliated cells in the nasal specimens, it is unlikely that all mucociliary transport would stop in these subjects if the ciliary machinery worked efficiently in one-third of the cells. The lack of coordination within the single cells seems the most likely explanation of the total absence of transport.

It is a prerequisite for a normal effective-recovery stroke that the dynein arms of certain microtubule doublets are sequentially activated, not only along the cilium but also around it (Machemer 1977). Our finding of cilia beating with normal frequency, but with reduced amplitude, and more resembling the arm of a metronome than of a crawling swimmer, is consistent with a partial defect in the equipment of dynein arms, possibly localized only to a segment of the cilium. If this preliminary interpretation is correct, the electron microscopic demonstration of normal arms does not exclude a partial defect incompatible with normal mucociliary function. Some dynein arms have in fact been demonstrated in patients with Kartagener's syndrome (Fig. 2) (Pedersen & Mygind 1976; Eliasson et al. 1977).

With the scraping method for obtaining ciliated cells from the nose, an electron microscopic examination is possible with all subjects; but this is a time-consuming procedure, generally restricted to research work. Repeated examinations of the mucociliary transport in the nose is easy, using the saccharine-dye method (Andersen et al. 1974), and a constant finding of absent transport is highly suggestive of 'immotile cilia syndrome'. But this test is unreliable in pre-school children and cannot be used in infants. As these methods were found not to be suitable for early diagnosis of the syndrome, we studied the living cells in vitro. Our first results have suggested that simple observation of a nasal scraping in a phase contrast microscope probably will in the future serve as a screening test for infants and children with chronic airway infections, as well as the sweat test for cystic fibrosis. The evidence also suggests that repeated examination after antibiotic therapy may be necessary for distinguishing the 'immotile cilia syndrome' from other chronic airway infections, as some airway pathogens are known to produce ciliotoxic substances (Reimer et al. 1978). However, it is obvious that a more detailed analysis of ciliary function and of the methods employed is necessary before any definite recommendations can be made regarding diagnosis for routine clinical use. Although the term 'immotile cilia syndrome' by now is widely used, we prefer 'ciliary dysfunction syndrome'. The term 'immotile cilia syndrome' is misleading in those Kartagener patients who have almost 100% motile cilia.

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PULMONARY LEIOMYOSARCOMAS

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Summary

Four cases of pulmonary leiomyosarcoma are presented. The characteristic histological features are described with specific reference to the criteria of malignancy. It is suggested that diagnosis by bronchoscopy provides insufficient material for histological grading and open lung biopsy is the diagnostic tool of choice. The available methods of treatment are discussed.

INTRODUCTION

Primary leiomyosarcomas are uncommon tumours in the lungs. They arise from smooth muscle present in the bronchi and blood vessels. All the case records of patients with pulmonary tumours diagnosed as sarcoma, leiomyoma and leiomyosarcoma at Brompton Hospital from 1955 to 1978 have been reviewed. Four cases of leiomyosarcoma were identified during this period and their features and treatment have been recorded in this article.

Case Reports

Case 1

A 63-year-old man, who had been a pipe smoker for 15 years, presented with a two-month history of exertional dyspnoea. On examination the only abnormal physical sign was finger clubbing. A chest radiograph showed bilateral patchy shadowing (Fig. 1). Other investigations revealed an ESR of 16 mm/hour, a negative tuberculin skin test, normal intravenous urogram, barium meal and follow through. Sigmoidoscopy to 17 cm was normal. Sputum cytology was negative for malignant cells.

A fibreoptic bronchoscopy revealed occlusion of a middle lobe subsegment by a submucosal swelling which was biopsied. An open lung biopsy was performed later on after receiving the report of the bronchoscopic histology.

The patient is alive and well on chemotherapy nine months after diagnosis.

Case 2

A 65-year-old man presented with an 18-month history of productive cough and weekly episodes of haemoptysis. He had been a pipe smoker until 13 months previously. On examination there were no abnormal physical signs.

A chest radiograph showed collapse and consolidation of the right lower lobe. His ESR was 60 mm/hour. Sputum cytology was negative for malignant cells. At rigid bronchoscopy an ulcerating tumour was seen in the middle lobe bronchus. The biopsy specimen consisted of necrotic material only.

A pneumonectomy was performed. The patient was alive and well with no evidence of recurrence six years after treatment.

Case 3

A 54-year-old housewife who had smoked 30 cigarettes a day for 30 years presented with a six-week history of malaise, left parasternal chest pain and weight loss of 6.3 kg. Examination revealed reduced air entry in the left upper zone. She had no finger clubbing or lymphadenopathy.

A mass at the left hilum was seen on chest radiograph. Her ESR was 24 mm/hour. Bronchoscopy showed no abnormality. At operation a tumour was removed from the left upper lobe and mediastinum. Dissection of the associated lymph nodes was also performed.

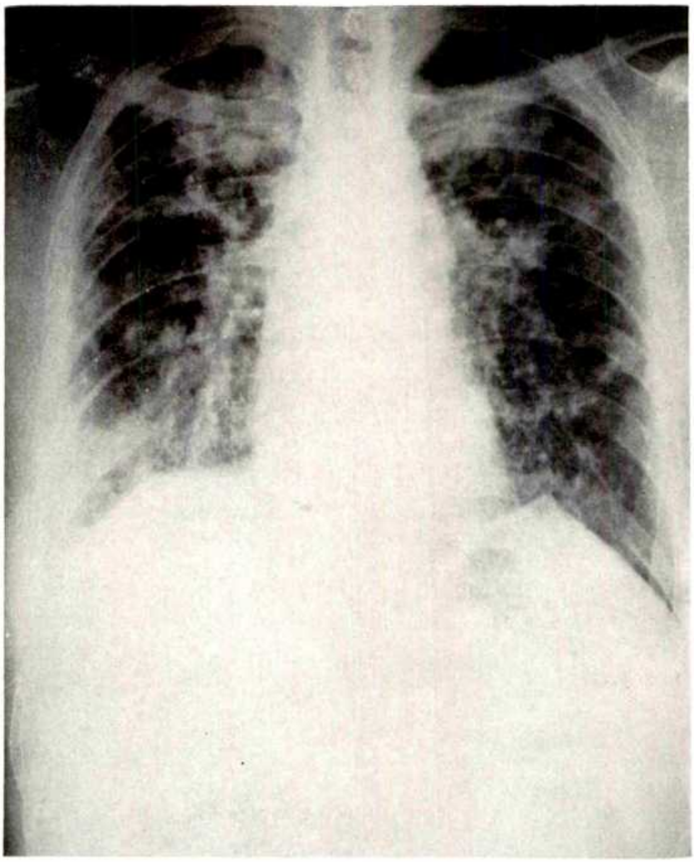

Fig. 1. Case 1. Chest radiograph showing bilateral nodular shadowing

Following surgery a radical course of radiotherapy was given. Fourteen months after treatment metastases developed in the scalp and manubrium sterni. These were initially treated with intermittent course of myleran and methotrexate but did not resolve. Nine months later metastases developed in the supraclavicular and axillary lymph nodes. The patient died three years after diagnosis. Autopsy was not performed.

Case 4

A 46-year-old Greek woman with a seven-year history of weight loss, malaise and back pain presented for investigation. Past history included a hysterectomy for a benign leiomyoma of the uterus in 1973 and admission to another hospital for investigation of weight loss in 1976; no gastrointestinal disease was demonstrated. The only abnormal findings were radiological features suggesting destruction of the ninth thoracic vertebra and a clinical diagnosis of tuberculosis was made. After one year's chemotherapy she returned to England for further investigation in 1978. Her chest radiograph now revealed extensive bilateral nodular shadowing. (Fig. 2).

On admission to hospital she had no respiratory symptoms. Examination failed to reveal any abnormal physical signs. The ESR was 9 mm/hour and barium studies were normal. Fibreoptic bronchoscopy was performed. Biopsy of the T9 lesion was carried out at a later date in another hospital.

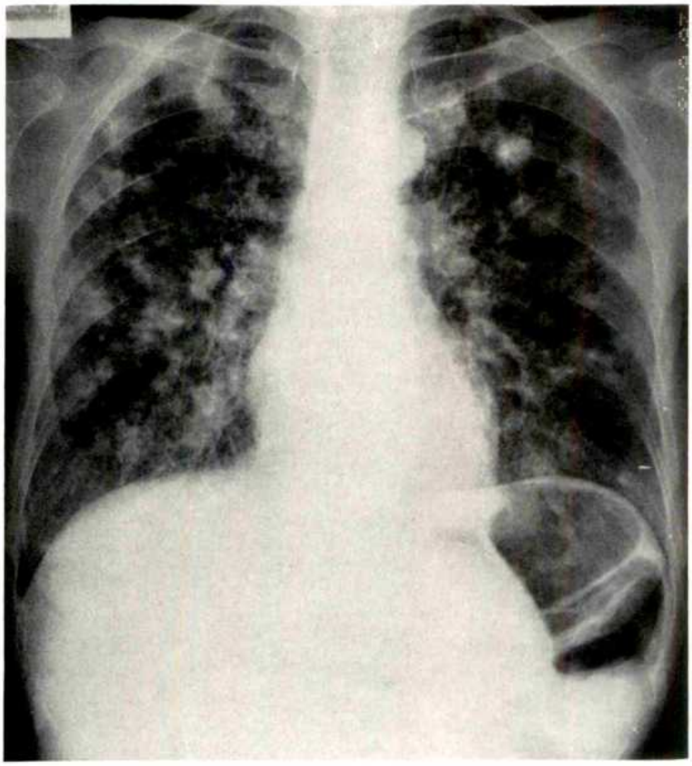

Fig. 2. Case 2. Chest radiograph showing bilateral nodular shadowing

HISTOPATHOLOGY

The histological material from these patients was all embedded originally in paraffin wax and stained by haematoxylin and eosin and a reticulin stain. As an aid to the identification of the cells of origin of the tumours, a selection of the following stains was used: elastic van Gieson, phosphotungstic acid haematoxylin and lissamine fast red. In our experience the lissamine fast red gave more reliable and consistent staining of myofibrils than the phosphotungstic acid haematoxylin stain.

The mean mitotic rate was assessed by counting the total number of mitoses in ten high power fields and calculating the average per high power field, at a magnification of 400.

Case 1. A bronchial biopsy obtained by fibreoptic bronchoscopy consisted of several small fragments of mucosa. The lamina propria of two of these pieces contained some tumour composed of spindle-shaped cells (Fig. 3) in which longitudinal myofibrils were demonstrated with lissamine fast red stain. The cells were arranged in irregular bundles and were separated by varying amounts of pale-staining intercellular substance. The cells showed a little pleomorphism and very occasional bizarre forms. A single mitosis was noted. A silver stain showed fine fibrils of reticulin closely related to individual cells. A transbronchial lung biopsy and an aspiration needle biopsy showed no abnormality.

An open lung biopsy was performed and the specimen included a segment of rib as well as a nodule from the lung, which measured 25 mm in diameter. It had a sharply defined edge and was of fleshy lung parenchyma away from bronchi; it was well-demarcated although there was no true capsule. The tumour cells were plump and spindle-shaped, showed marked pleomorphism, many bizarre forms and were arranged in interwoven bundles. The mean mitotic rate was ten per high power field. The rib biopsy showed similar tumour issue invading bone.

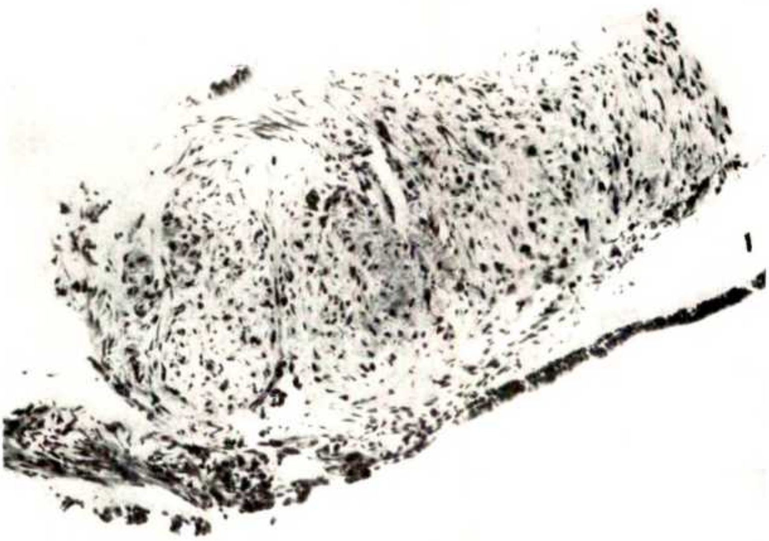

Fig. 3. Case 1. A small fragment of bronchial mucosa showing whorled groups of pleomorphic spindle cells. H & E ×125

Case 2. A polypoid tumour was present occluding the proximal parts of the middle and lower lobe bronchus of the right lung. The lung distal to the obstruction showed severe bronchiectasis and foci of consolidation.

The tumour was highly cellular, being composed of spindle-shaped cells arranged in bundles and whorls. Small foci of necrotic tissue were present (Fig. 4). The cells showed moderate pleomorphism and scattered plump cells with large, bizarre nuclei were noted throughout the tissue. The mitotic rate was 8.6 per high power field. The sections were stained by elastic van Gieson and reticulin stains. They revealed a small amount of mature collagen and reticulin fibres arranged in fine strands closely associated with individual tumour cells. Tumour was not present within the lymph nodes.

Case 3. The surgical specimen was a tumour 100×60 mm in the left upper lobe extending into the mediastinum.

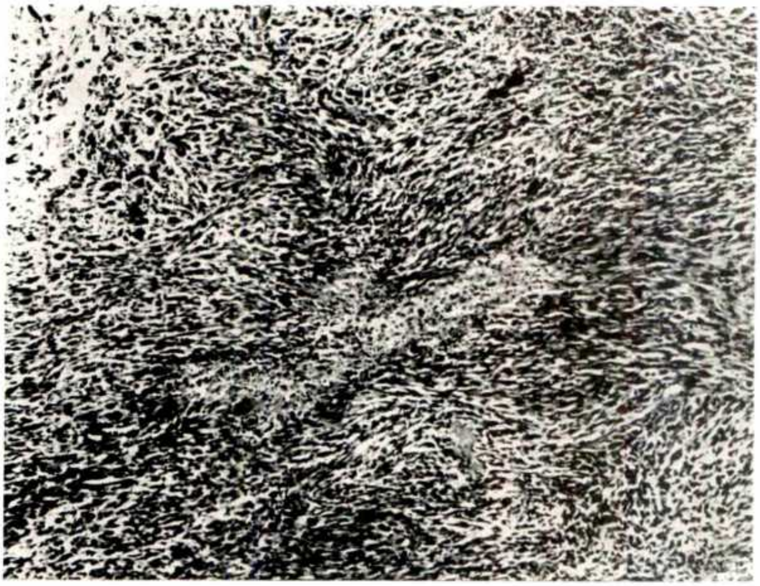

Fig. 4. Case 2. Section of resected tumour showing bundles of spindle-shaped cells and a small focus of necrosis. H & E ×80

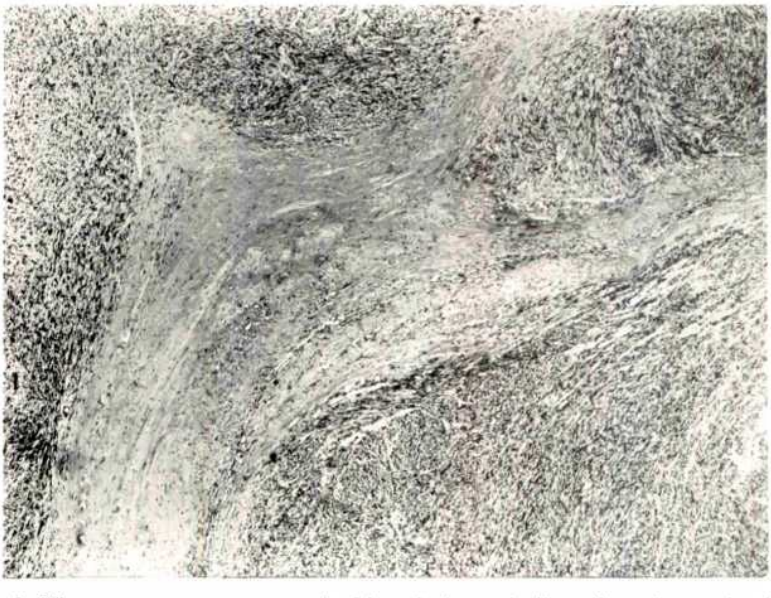

Fig. 5. Case 3. The tumour was composed of interlacing spindle cells and contained large bands of fibrosis. H & E ×25

The tumour was divided into lobules by bands of fibrous connective tissue (Fig. 5). It was well-delineated from the surrounding tissue but did not have a true capsule. The tumour cells were spindle-shaped and arranged in whorls. There was very little material between the cells although scattered foci of intercellular oedema were noted. Scattered bizarre and multinucleated cells were found and the mitotic rate was estimated to be 1 per high power field.

A phosphotungstic acid haematoxylin stain revealed longitudinal intracytoplasmic myofibrils (Fig. 6) confirming the smooth muscle nature of the tumour. A silver stain showed fine reticulin fibrils surrounding individual cells. An elastic van Gieson stain showed only a small amount of mature collagen and the tumour cells showed uniform staining characteristics.

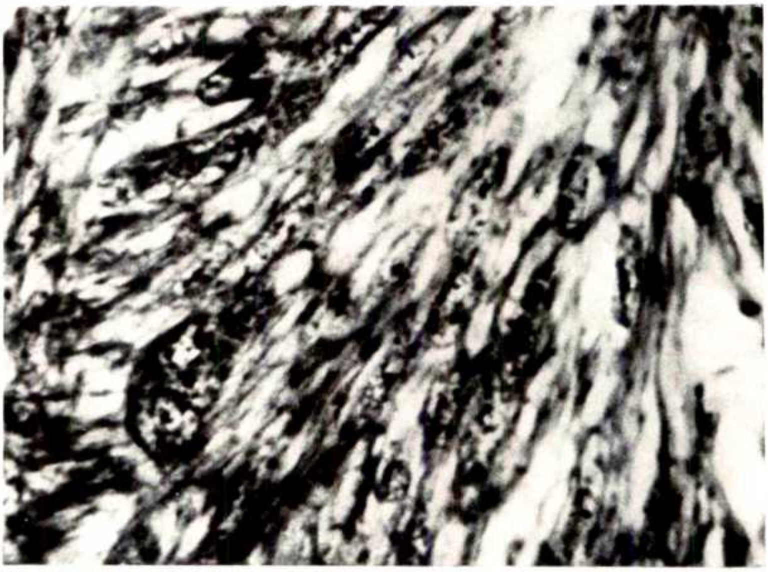

Fig. 6. Case 3. The longitudinal myofibrils in the spindle-shaped cells are best seen adjacent to the large bizarre nucleus in the lower left field. PTAH approx. × 720

Case 4. The specimen was a small fragment of tissue obtained by transbronchial biopsy through a fibreoptic bronchoscope. Histologically there were several pieces of pulmonary tissue (some alveoli containing small collections of haemosiderin-laden macrophages) and separate fragments of tumour composed of spindle-shaped cells arranged in loose whorls. There was little pleomorphism within the cells and no bizarre forms were noted. No mitoses were seen in the biopsy. The abnormal cells were shown to contain myofibrils by staining with the lissamine fast red method.

DISCUSSION

Primary leiomyosarcoma is a rare tumour mostly of adults although it has very occasionally been reported in children (Merrit & Parker 1957). It resembles carcinoma of the bronchus in its symptomatology, physical signs and radiology—and this is confirmed in our cases. Clubbing is an unusual feature and has been described previously in only three cases (Ramanathan 1974). Histological examination is the most reliable method of diagnosis and differentiation from carcinoma. Sputum cytology is found to be generally negative.

The two important questions to be answered in reaching the diagnosis are whether the tumour is primary or secondary in the lung and how the tumour will behave. The first question can be answered with certainty only in the autopsy room, but a preliminary clinical diagnosis may be provided by a careful examination of the soft tissues, grastrointestinal tract and genitourinary tract. In Cases 2 and 3 the tumour undoubtedly arose in the lung. In Case 1, however, the presence of bilateral disease suggested metastatic malignancy. A full investigation of the likely primary sites revealed no sign of any alternative origin in the lung. So far, only one authenticated case of primary bilateral pulmonary leiomyosarcoma has been reported (Hicks 1957) and this case had similar presentation and findings to our patient.

It has been suggested that leiomyosarcoma in the lung in female patients should never be considered as a primary neoplasm. There is a high incidence of smooth muscle tumours in the uterus and although the majority of these behave in a benign fashion, metastases from tumours with histological characteristics of leiomyomas have been described (Spiro & McPeak 1966), the 'benign metastasizing leiomyoma'. The dilemma of the tumour metastasizing to the lung was first described at Brompton Hospital (Burrell & Ross 1937). Case 4 illustrates this problem; the patient had had a hysterectomy for benign leiomyoma four years before presentation. Unfortunately the original uterine histology was not available for review. Radiographs revealed abnormalities due to metastatic leiomyosarcoma in both lungs and in a vertebral body.

Predicting the behaviour of leiomyosarcomas is difficult. Certain markers of malignancy have been studied in soft tissue sarcomas and it was found that, of various criteria investigated (the site of the tumour, cellular pleomorphism, presence of bizarre cells, mitotic rate and intracellular myofibrils), the mitotic rate correlated best with the behaviour of the tumours (Stout & Hill 1958). In three of our cases (Cases 1, 2 and 3) a large portion of tumour was available for study and mitotic rate was counted with a fair degree of reproducibility. In Case 3, even though the mitotic rate was low, survival was shorter than in Case 2. This can perhaps be explained as the tumour was large, had already invaded the mediastinum and had many bizarre cells.

Bronchoscopic biopsies only were available for the initial diagnosis in Case 1 and were the only tissue available in Case 4. It was clear that in such small pieces of tissue the mitotic rate could not be measured accurately. In view of the widespread use of fibreoptic bronchoscopy in the diagnosis of lung disease and the likelihood of this situation occurring more frequently in the future, all the above-mentioned criteria must be taken into consideration when assessing the malignancy of tumours. Furthermore, if there is still histological doubt or clinical suspicion of malignancy, an open lung biopsy should be performed.

Although metastases to lymph nodes have been described previously (Tocker et al. 1957; Agnos & Starkey 1958), it is an unusual feature of pulmonary leiomyosarcoma. Only one of our patients (Case 3) developed lymph-node involvement. Metastases have also been described in the liver (Agnos & Starkey 1958; Dyson & Trentalance 1964; Mason & Azeem 1965), pleura (Watson & Anlyan 1958; Hering et al. 1962; Ramanathan 1974), skin (Tocker et al. 1957) and adrenal glands (Agnos & Starkey 1958; Mason & Azeem 1965).

Three modes of treatment have been used in the management of pulmonary leiomyosarcomas: surgery, radiotherapy and chemotherapy. In limited disease surgery is undoubtedly the treatment of choice although Guccion and Rosen (1972) described extension into the chest wall, mediastinum and diaphragm in 11 of 15 cases. Three-year survival figures of 22% have been reported (Ramanathan 1974) and there are reports of patients surviving 16 years after surgery (Ochsner & Ochsner 1958). In our series Cases 2 and 3 underline the value of surgery.

Radiotherapy has been used only palliatively: indeed in the treatment of sarcomas results have been disappointing (Cheng 1977). For bilateral disease or extrathoracic dissemination chemotherapy has been advocated. Until 1970 the results were poor. Since DTIC (dimethyl thiazine imidazole carboxamide) and adriamycin were introduced into the chemotherapeutic schedules, with response rates of 21% and 25% respectively, 43% five-year survival of all types of leiomyosarcoma has been reported (Cheng 1977).

Adjuvant immunotherapy has been suggested for its augmentative therapeutic effect but so far experience has been limited (Townsend et al. 1976). In view of the rarity of these tumours it is difficult to compare different therapies and a multi-centre trial would be useful as a means of assessing management of this disease.

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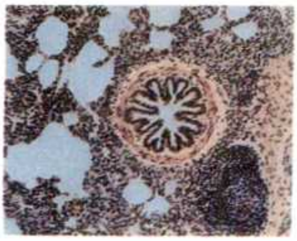

Cross-section of bronchiole illustrating bronchospasm due to contraction of respiratory smooth muscle.

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(*Modern Medicine*, May, 1977, p. 57-58)

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ICATIONS

tine control of bronchospasm in bronchial asthma, bronchitis and emphysema, or as uired to relieve attacks of acute bronchospasm. Doses may also be taken before exertion revent exercise induced asthma or before exposure to a known unavoidable challenge

SAGE AND ADMINISTRATION

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ldren: one Ventolin Rotacap 200mcg three or four times a day

optimum results in most patients inhaled Ventolin should be administered regularly

NTRA-INDICATIONS

tolin preparations should not be used for the prevention of threatened abortion

ECAUTIONS

previously effective dose of inhaled Ventolin fails to give relief lasting at least 3 hours, patient should be advised to seek medical advice. Ventolin should be administered tiously to patients suffering from thyrotoxicosis. Unnecessary administration of drugs ing the first trimester of pregnancy is undesirable

E EFFECTS

important side effects have been reported following treatment with inhaled Ventolin

ODUCT LICENCE NUMBERS

ntolin Inhaler 0045/5022, Ventolin Rotacaps 200mcg 0045/0116,
ntolin Rotacaps 400mcg 0045/0117

PRODUCT INFORMATION

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Becotide Rotahaler, for use in conjunction with Becotide Rotacaps. Basic NHS cost 78p.

INDICATIONS

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DOSAGE AND ADMINISTRATION

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Children: one or two inhalations, two, three or four times a day according to the respons
Using Becotide Rotahaler – *Adults:* one 200mcg Becotide Rotacap three or four times a day is the usual maintenance dose.
Children: one 100mcg Becotide Rotacap, two, three or four times a day according to the response

For optimum results inhaled Becotide should be administered regularly

CONTRA-INDICATIONS

No specific contra-indications to inhaled Becotide are known but special care is necessa in patients with active or quiescent pulmonary tuberculosis

PRECAUTIONS

The maximum daily intake of beclomethasone dipropionate BP should not exceed 1mg. Inadequate response after the first week of inhaled Becotide therapy suggests that excessive mucus is preventing penetration of inhaled drug to the target area. A short cou of systemic steroid in relatively high dosage should be given and therapy with inhaled Becotide continued.

Unnecessary administration of drugs during the first trimester of pregnancy is undesirat When transferring patients to Becotide from systemic steroid therapy the possibility of adrenocortical suppression should be considered and patients given a supply of oral steroids for use during periods of stress. Please refer to the detailed procedure describec the data sheets for Becotide Inhaler and Becotide Rotacaps

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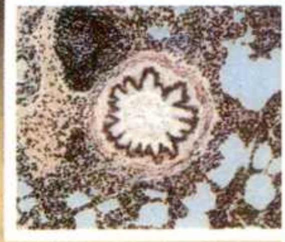

Cross-section of bronchiole illustrating bronchospasm complicated by bronchial mucosal oedema and hypersecretion of mucus.

> "To support this claim of extraordinary activity (of Becotide), there are not only statistically valid comparisons but also numerous validated individual experiences. These include the impressive therapeutic results in patients with severe asthma not controllable with high daily doses of systemic steroids; the beneficial responses of those refractory to adrenergic agonists and unable to tolerate even suboptimal doses of theophylline; the suppression of asthma unresponsive to mediator-release inhibitors, such as cromolyn sodium; and, importantly, the high level of acceptance and compliance among people who do not comply with other standard therapeutic routines"
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1. M McNicol Jnl. Roy. Coll. Phys. of Lond. (1979) 13, 1.

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Br. J. Dis. Chest (1980) *74*, 253

THE VALUE OF A WIDE RANGE OF TESTS IN THE ASSESSMENT OF LUNG FUNCTION IN CARCINOMA OF THE BRONCHUS

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Summary

Tests of forced ventilation, lung volume, transfer factor, flow-volume and arterial blood gas measurements were made on 209 patients before thoracotomy for carcinoma of the bronchus. The patients whom the surgeons subsequently considered to be unsuitable for operation had significantly poorer results in tests of forced ventilation than those who were selected for operation. There was little or no significant difference between these groups in respect of the RV, TLC, transfer factor and arterial blood gas measurements. There was no marked difference in the results of any of the measurements between those who developed complications and those who were complication free. It was therefore concluded that clinical assessment together with forced ventilation tests could not be bettered by adding further lung function tests, when these were interpreted as simply 'normal or abnormal'. However, more complex analysis of test findings, such as discriminant analysis, may be of more value.

INTRODUCTION

The determination of the functional state of the lungs using widely available tests has become a standard part of the assessment of patients before thoracotomy for carcinoma of the bronchus (Mittman & Brüderman 1977). Most thoracic surgery centres have some means of carrying out at least the simple forced ventilation tests. Although perhaps not performed on every patient, formal tests are done whenever dysfunction of the rest of the lung field is suspected, either from the clinical examination and history or from other preoperative investigations such as radiography and bronchoscopy.

The principles of interpreting basic lung function test results in this context were established in the days of the great expansion of chest surgery. They are widely recognized today and in some centres are embodied in schemes for classifying patients according to the risk of postoperative complications (Lockwood 1980). The present investigation was carried out to see if more recently introduced lung function measurements could improve selection of patients over what is already accomplished using the simple tests and clinical assessment. Additional measurements from the expiratory spirogram, the flow–volume curve, the transfer factor for carbon monoxide and arterial blood gas estimation are all procedures commonly carried out in respiratory function laboratories today (Clarke 1976) and are likely to be requested by the clinician making the surgical decision.

Material and Methods

Lung function tests were performed on as many as possible of the patients with carcinoma of the bronchus who were admitted to the Thoracic Surgical Unit at Harefield Hospital in 1977. 209 patients were studied and lung volume, forced ventilation and as many of the other procedures as time allowed were carried out for each.

Each patient was ultimately classified into one of three groups:

Group I: those operated on who suffered postoperative cardiopulmonary complications
Group II: those operated on who were free from complications
Group III: those who were considered unsuitable for operation by the surgeons

The decision about operating was made after the results of the tests were known and was therefore influenced by the test findings.

The distinction between the presence and absence of complications was not always clear. Accordingly any patient about whom there was doubt was excluded from the survey. There were nine such patients who had slightly uneasy postoperative courses with transient cough and sputum production, or atrial fibrillation and ankle oedema, for example, which reverted without special measures being taken. The progress in each case was noted as 'uneventful' in the medical records, although at the time there were suspicions on the part of the nursing staff and physiotherapists (with whom constant contact was maintained) that a more major complication might develop.

The lung function measurements made were as follows:

Forced ventilation tests were carried out on a water spirometer (Bernstein et al. 1952), yielding values for the FVC, FEV_1 and MVV (by direct measurement over 10–20 seconds). The MMFR (Leuallen & Fowler 1955) and $FEF_{75-85\%}$ (Morris et al. 1975) were also measured.

The lung volumes and the single-breath transfer factor ($T_{CO}SB$) were determined using the Morgan Resparameter (Meade et al. 1965), the values recorded for the FRC and the $T_{CO}SB$ being the average of two determinations and the other lung volumes being calculated using the larger of the two VC recordings obtained at the completion of each helium dilution test. The helium mix-in time was noted as the time between the commencement of the volume measurement and the stabilization of the helium concentration in the apparatus, the larger of the two being recorded as the 'mixing time'.

The flow–volume loop was obtained with an Ohio dry spirometer and a Bryans XY recorder, from which standard measurements were made (Bass 1973). Whilst attending for these tests, blood samples were taken from the brachial artery into heparinized disposable syringes and analysed immediately in an Instrumentation Laboratory IL 413 blood gas analyser.

RESULTS

Table I shows that there were 41 patients in Group I with some heart or lung condition for which special treatment had to be instituted. Seven died as a result of their conditions during the immediate postoperative period.

Table I. Complications suffered by patients in Group I with the number of resulting deaths before discharge from hospital

Complication	*No. of patients*	*No. of deaths*
Sputum retention	6	—
Respiratory failure	10	2
Heart conditions	13	3
Bronchopleural fistula	10	2
Haemothorax	2	—

The mean and standard deviation of each of the results in the three groups is given in Table II, which also shows the significance of the differences between the group means by the Student's *t*-test.

It can be seen that no difference is revealed by this analysis between the patients with and those without complications (Groups I and II), except in the arterial P_{O_2} values where there is a difference at a low level of significance.

The forced ventilation test results in Groups I and II who had operations were significantly better than those in Group III who were not operated on. The RV, TLC, K and arterial blood gas values showed little or no significant difference between these groups. Group I shows a significant difference in the mixing time from Group III whilst Group II does not. Group II shows a significant difference in the FEF and T_{CO}SB from Group III whereas Group I does not.

DISCUSSION

The aim of carrying out respiratory function tests, and thereby revealing pulmonary dysfunction in addition to that due to the operable lesion, is to reduce the incidence of postoperative complications or severe breathlessness. The risk of death due to complications after thoracotomy is not directly related to the preoperative functional state (van Nostrand et al. 1968; Lockwood 1972). However, the complications referred to are related to preoperative function.

For the purposes of a study such as this a postoperative complication can be defined as 'an abnormal condition of the heart or lungs, attributable directly to the preceding operation, of a degree sufficient to require an alteration in treatment'.

The relationship between the complications listed in Table I and preoperative test results were studied by Lockwood (1973). Bronchopleural fistula was the complication found to have the greatest statistical relationship whilst pulmonary embolism, pleurisy and empyema were shown to be unrelated. Although a relationship between abnormal lung function and complications other than primary respiratory insufficiency has been questioned (Gaensler et al. 1955), other authors have suggested that the occurrence of heart complications and bronchopleural fistulae may be associated with poor preoperative test findings (Hirdes & Bosch 1955; Bryant et al. 1970). The crux seems to be the distinction between a causal relationship and a statistical relationship. The latter can exist and be of value in the prediction of the risk of the complication in its own right without implying a causal relationship.

Any laboratory actively involved in carrying out tests as part of a preoperative selection procedure is constantly seeking to improve the application of the tests and their results. There is therefore a tendency to carry out extra tests whenever newer ones become available.

The present investigation was instigated to see if simple statistical treatment would indicate which of the common lung function tests available today could be shown to be useful in this context. Improvement in the clinical assessment and the restriction of surgery to certain types of lung tumour has altered the situation from the time 20 or 30 years ago when this application of respiratory function tests was first widely investigated.

It is immediately obvious from an examination of Table II that many of the test

Table II. Means and standard deviations of the respiratory function test results in the three groups of patients and the significance of the differences between the means by the students *t* test

	Group I: patients with complications		*Group II: patients without complications*		*Group III: patients not operated on*		*Grade of significance of differences between groups**		
	Mean (SD)	No. tested	Mean (SD)	No. tested	Mean (SD)	No. tested	I and II	I and III	II and III
Age (years)	60.5 (6.6)	41	62 (6.1)	93	65.6 (6.1)	66	—	2	—
VC (litres)	3.4 (1.0)	41	3.4 (0.8)	93	2.8 (0.9)	66	—	2	3
FVC (litres)	3.3 (1.0)	41	3.3 (0.8)	93	2.7 (1.0)	66	—	2	3
RV (litres)	1.7 (0.6)	41	1.5 (0.6)	93	1.7 (0.7)	66	—	—	1
TLC (litres)	5.2 (1.5)	41	5.0 (1.1)	93	4.7 (1.2)	66	—	—	—
RV/TLC (%)	33 (9.5)	41	30 (8.6)	93	37 (11.6)	66	—	1	3
FEV_1 (litres)	2.2 (0.7)	41	2.2 (0.6)	93	1.7 (0.6)	66	—	3	3
FEV_1/FVC (%)	66 (11)	41	68 (11)	93	61 (11)	66	—	1	3
MVV (litres/minute)	78 (33)	41	76 (24)	93	57 (24)	66	—	3	3
Mixing time (seconds)	151 (39)	41	165 (45)	93	175 (45)	66	—	2	—

MMFR (litres/second)	1.6 (1.1)	41	1.7 (0.9)	93	1.1 (0.5)	66	—	2	3
FEF$_{75-85\%}$	0.5 (0.4)	41	0.5 (0.3)	93	0.3 (0.1)	66	—	—	2
T$_{CO}$SB (ml CO/min/mmHg)	23 (8)	33	21 (5)	74	19 (6)	59	—	1	2
K (minutes)	3.3 (0.8)	35	3.3 (0.7)	82	3.3 (1.0)	53	—	—	—
Values from the flow-volume trace									
Max. expiratory flow rate	6.5 (2.2)	32	5.9 (1.5)	79	5.0 (1.7)	56	—	3	2
Flow at 25% (litres/second)	4.9 (2.7)	31	4.3 (2.0)	71	3.2 (1.1)	56	—	2	3
Flow at 50% VC (litres/second)	2.2 (1.2)	32	2.1 (1.1)	79	1.5 (0.7)	56	—	2	3
Flow at 75% VC (litres/second)	0.7 (0.4)	32	0.7 (0.3)	79	0.5 (0.2)	56	—	2	3
Arterial blood									
P_{O_2} (kPa)	9.4 (0.9)	18	10.0 (1.1)	48	9.5 (1.0)	37	1	—	—
P_{CO_2} (kPa)	5.0 (0.5)	18	5.3 (0.5)	48	5.3 (0.6)	37	—	—	—

* — = not significant ($P > 0.05$); 1 = $P = 0.05$–0.01; 2 = $P = 0.01$–0.001; 3 = $P < 0.001$.

results distinguish between those operated on (Groups I and II) and those not operated on (Group III), but that there are few differences between results of tests in groups I and II. Thus any convenient measurement or set of related measurements showing significant differences at the highest levels will contribute as much as a wider array of measurements to the surgical decision. Those from the spirogram tracing of the FVC (in particular the FEV_1 and MMFR) and the MVV are the best examples, followed by the flow measurements from the flow–volume trace. The lung volumes are not even an alternative to the forced ventilation measurements and certainly contribute nothing further to distinguishing between the groups when used in the simple way indicated here.

It can be concluded that a wider range of lung function measurements does not help in the identification either of those patients who are unsuitable for surgery or of those who will suffer postoperative cardiopulmonary complications even though they satisfy the present-day criteria for selection for surgery. It must be admitted that this conclusion is based on the discriminating power of the individual results and does not necessarily exclude their use in multivariate analysis, an approach that deserves further investigation.

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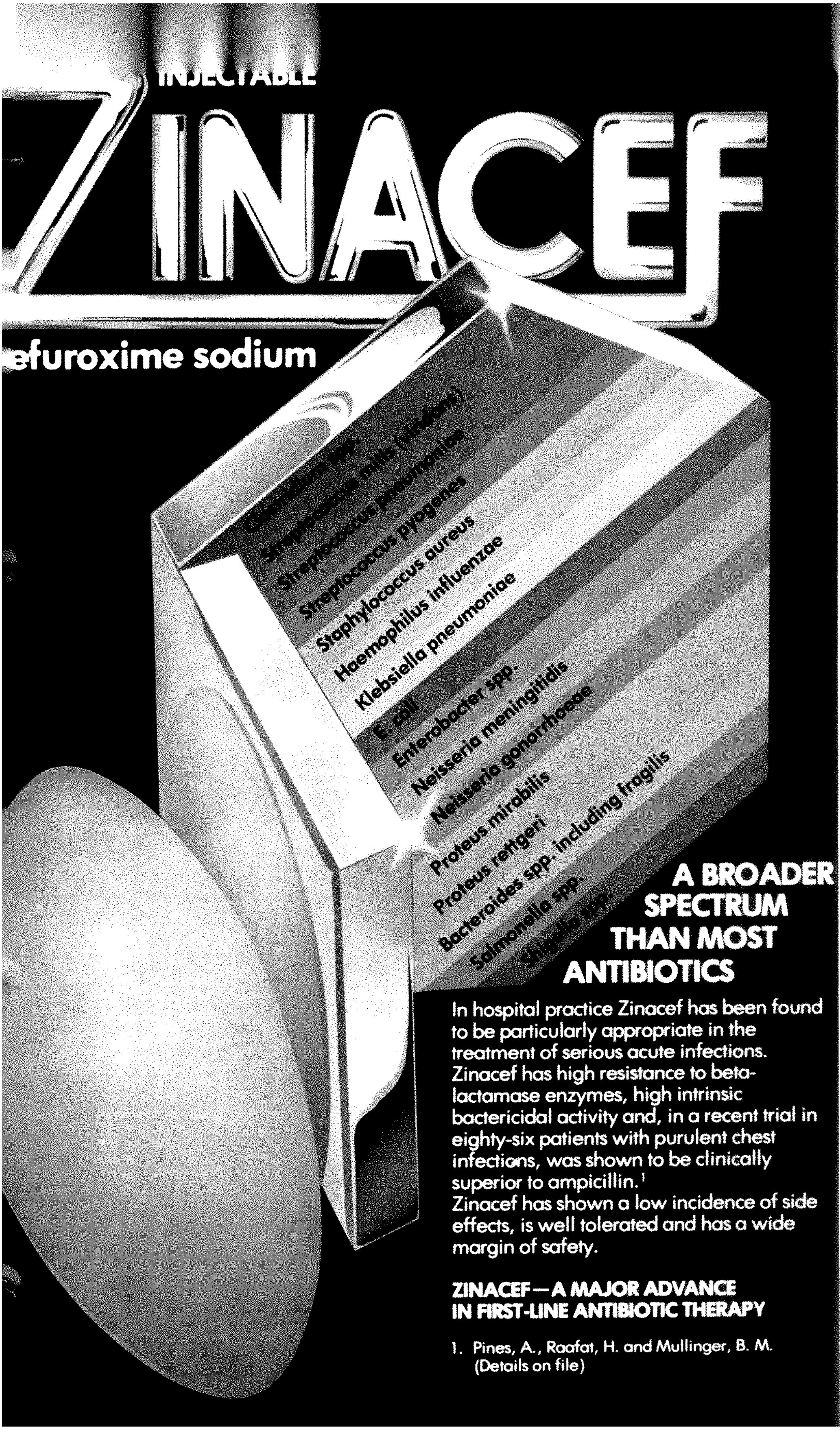

A BROADER SPECTRUM THAN MOST ANTIBIOTICS

In hospital practice Zinacef has been found to be particularly appropriate in the treatment of serious acute infections. Zinacef has high resistance to beta-lactamase enzymes, high intrinsic bactericidal activity and, in a recent trial in eighty-six patients with purulent chest infections, was shown to be clinically superior to ampicillin.[1]
Zinacef has shown a low incidence of side effects, is well tolerated and has a wide margin of safety.

ZINACEF—A MAJOR ADVANCE IN FIRST-LINE ANTIBIOTIC THERAPY

1. Pines, A., Raafat, H. and Mullinger, B. M. (Details on file)

Prescribing information

Presentation
Vials of 250mg, 750mg and 1.5
and infusion pack of 1.5 grams
containing cefuroxime as cefuro
sodium.

Indications
Serious bacterial infections, esp
where the causative organisms h
yet been identified.

Conditions include:
Chest infections
Septicaemia
Soft tissue infections
Obstetric and gynaecological i
Bone and joint infections
Ear, nose and throat infection
Meningitis
Gonorrhoea

Dosage
Adults: Generally 750mg t.i.d. i
Severe infections 1.5 grams t.d
Frequency of injections can be i
to six hourly if necessary, giving
doses of 3 grams to 6 grams dai

Infants and children: 30 to 100mg
in three or four divided doses.
60mg/kg/day will be appropriat
most infections.

Neonates: 30 to 100mg/kg/day i
three divided doses.

Gonorrhoea: Single dose of 1.5 g
750mg i.m. into different sites

Contra-indications
Hypersensitivity to cephalosporin

Precautions
Cephalosporins may in general
safely to patients who are hypers
to penicillins.
As with all drugs, Zinacef should
administered with caution durin
early months of pregnancy.
Zinacef does not interfere with e
based tests for glycosuria.
Cephalosporins interfere with te
glycosuria which use copper red
ferricyanide methods and with t
alkaline picrate assay for creatin
with other antibiotics, prolonged
result in the overgrowth of non
susceptible organisms.
Zinacef should not be mixed in t
syringe with aminoglycoside anti
Reduce dosage when renal func
markedly impaired.
Cephalosporins at high dosage s
given with caution to patients re
concurrent treatment with poter
diuretics such as frusemide, as t
combinations are suspected of a
affecting renal function. Clinical
experience with Zinacef has sho
this is not likely to be a problem
recommended dose levels.

Side effects
Adverse reactions are rare and g
mild and transient, e.g. rashes,
intestinal disturbance, candida
decreased haemoglobin concent
eosinophilia, a positive Coombs
transient rises in serum liver enz
transient pain after i.m. injectio

Storage
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5 x 250mg £0.70 per vial
5 x 750mg £2.10 per vial
1.5 grams £4.20

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Chris Drury. World Champio
arsman and asthmatic.

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In fact, between the ages of 7 and 10, he was regarded as being to ill even to participate in school sport

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Fisons Limited, Pharmaceutical Division, Derby Road, Loughborough, Leicestershire. LEll 0BB. **Dosage and administration**: Intal and Intal Compound are presentations of Sodium Cromoglycate 20mg in the form of Spincaps*. Intal Compound also contains Isoprenaline Sulphate 0.1mg. Intal and Intal Compound are inhaled using a specially developed inhaler, the Spinhaler*, which works through the patients own inspiratory effort. Since therapy with Intal and Intal Compound is preventive, it is important that the patient is instructed to maintain regular dosage as distinct from inhaling the drug intermittently to relieve symptoms. The normal dose is 4 Spincaps daily to be taken at regular intervals. It may be necessary to increase this to 6 to 8 daily in more severe cases or during periods of severe antigen challenge. **Precautions**: for Intal Compound the precautions normally applying to Isoprenaline should be observed. **Side effects:** occasional irritation of the throat and trachea may occur. **Overdosage:** no action other than medical observation should be necessary.

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COMPARISON OF ATROPINE WITH IPRATROPIUM BROMIDE IN PATIENTS WITH REVERSIBLE AIRWAYS OBSTRUCTION UNRESPONSIVE TO SALBUTAMOL

P. SHERWOOD BURGE,* MARK G. HARRIES AND ELIZABETH I'ANSON

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Summary

Dose–response curves for atropine and ipratropium bromide were made in nine asthmatics unresponsive to salbutamol. Conventional doses of ipratropium resulted in significantly less bronchodilatation than large doses of atropine, suggesting that larger doses of ipratropium should be used.

INTRODUCTION

Selective sympathomimetic drugs produce satisfactory bronchodilatation in the majority of asthmatics. There remains a small number of patients who have a history of reversible airways obstruction who fail to respond to these drugs. It is in these non-responders that alternative drugs are required. Atropine may improve lung function temporarily in this group, but is unsuitable for prolonged treatment because of its unpleasant side effects, the possible harm from drying secretions and tachyphylaxis. Ipratropium bromide has been developed as a practical anticholinergic drug (Englehardt & Klupp 1975; von Bauer et al. 1976). It does not have systemic effects at the recommended dosage of 18–36 μg, three to four times daily and produces a degree of bronchodilatation similar to isoprenaline in patients responding to isoprenaline (Storms et al. 1975; Baigelman & Chodosh 1977; Chervinsky 1977) but there have been no previous studies of ipratropium in patients who fail to respond to sympathomimetic drugs. We have studied a group of asthmatics unresponsive to 200 μg salbutamol. In this group we have compared the response to atropine methonitrate and ipratropium using successive doses of each drug.

Patients and Methods

Nine chronic asthmatics (ages 34–63) were studied. They were selected because of lack of subjective response to bronchodilator aerosols and because 200 μg of salbutamol inhaled from a pressurized aerosol produced less than 15% improvement of FEV$_1$.

On randomly allocated successive days each patient was given salbutamol or atropine methonitrate or ipratropium by inhalation. All tests were started at 1400 hours; bronchodilators were stopped more than 12 hours before testing, but corticosteroids (in the seven taking them) were left unaltered. After base-line measurements of airways resistance (R$_{aw}$), total lung capacity (TLC), FEV$_1$ and FVC, the first dose of the selected bronchodilator was given. Atropine was inhaled after nebulization in a Wright's nebulizer, very approximately 1.5 mg being inhaled on each occasion. Ipratropium and salbutamol were given from metered dose inhalers; 40 μg ipratropium or 200 μg salbutamol were given on each occasion. Three doses of each drug were given, with repeat measurements of R_{aw}, TLC and FEV_1 20 minutes after each dose of atropine and ipratropium, and ten minutes after each dose of salbutamol. In this way about 4.5 mg atropine, 120 μg ipratropium and 600 μg salbutamol were given. Airways resistance was converted to its reciprocal conductance and expressed as a ratio to thoracic gas volume, specific conductance (SG_{aw}).

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RESULTS

Table I shows the values for FEV_1, specific conductance and total lung capacity before and after three doses of each drug. Atropine resulted in the highest FEV_1 and specific conductance in every patient ($P < 0.01$, signed rank test). The greatest reduction in total lung capacity followed atropine in seven out of nine (signed rank test not significant). The dose response graphs for FEV_1 are shown in Fig. 1. FEV_1 continued to rise after the third dose of atropine and ipratropium, but reached a plateau after salbutamol; however, the FEV_1 after the third dose of ipratropium was less than after the first dose of atropine. The dose–response curves for specific conductance and total lung capacity were similar, a plateau being reached after the first dose of salbutamol, but an increasing effect occurring with each dose of ipratropium and atropine. There was no significant change in pulse or blood pressure after any of the drugs. Atropine caused severe dryness of the mouth in most patients; two patients had only one inhalation of atropine because of this. One patient developed chest pain after atropine. Ipratropium produced no systemic effects, and although four patients said the taste was unpleasant the remaining five were unable to taste the drug.

Table I. Mean FEV_1, SG_{aw} and TLC before and after three doses of atropine, ipratropium bromide and salbutamol

	FEV_1 (litres)		*SG_{aw}* (sec/kPa)		*TLC* (litres)	
	Before	After three doses	Before	After three doses	Before	After three doses
Atropine	1.1	1.56	0.47	1.32	6.85	6.27
Ipratropium bromide	1.19	1.37	0.64	1.05	6.88	6.42
Salbutamol	1.28	1.38	0.54	1.19	6.68	6.49

DISCUSSION

In patients unresponsive to beta-adrenergic stimulants atropine is a superior drug to ipratropium for producing maximal bronchodilatation in the dosage used. The dose of atropine used was large and unsuitable for continuous use, but it does demonstrate that in these patients, who have fixed airways obstruction on conventional criteria, useful bronchodilatation can be achieved.

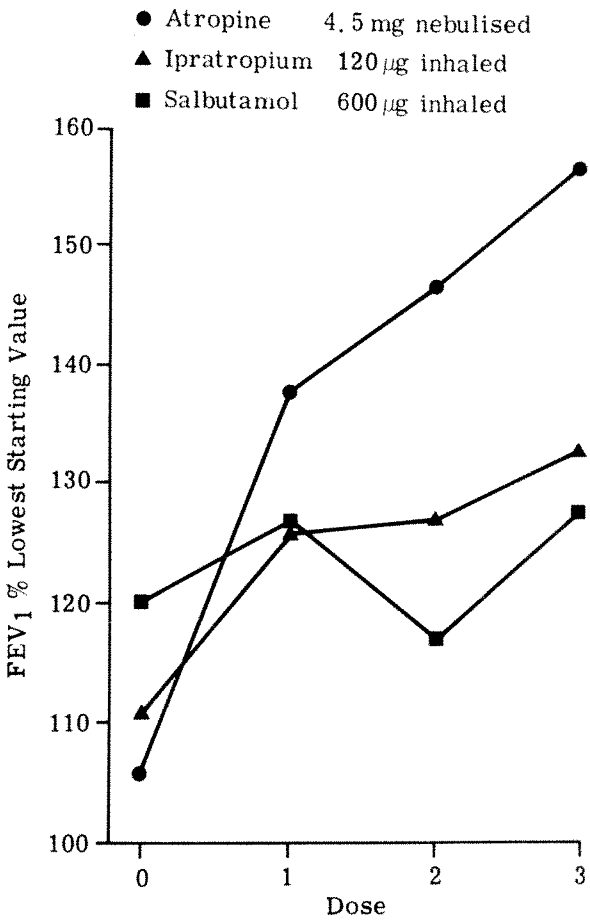

Fig. 1. Dose–response curve for atropine, ipratropium bromide and salbutamol. Results of FEV_1 are expressed as a percentage of the lowest starting value in each patient. (As there were small differences in the starting values, the mean starting value for each drug is greater than the lowest starting value)

Dose–response curves for ipratropium have shown little additional improvement after 20 µg by inhalation (Bauer & Kummer 1975), although all parameters in our patients appeared to be continuing to improve at 120 µg.

Ipratropium has been developed to try and dissociate the anticholinergic effects on the respiratory tract from other effector organs in the gastrointestinal tract, central nervous system and sweat glands (Deckers 1975). It is possible, however, that the lack of side effects is due to the low dose generally used. It would seem reasonable to give substantially larger doses of ipratropium to asthmatics unresponsive to sympathomimetics.

ACKNOWLEDGEMENTS

We would like to thank Dr F. J. Prime for his considerable help and Miss M. Rehahn for her help with the statistics.

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UPPER LOBE FIBROSIS AND CAVITATION IN RHEUMATOID DISEASE

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Summary

Four patients are described with rheumatoid disease with upper lobe fibrosis and cavitation which could not be explained by cavitation of rheumatoid nodules or any other recognized pulmonary manifestation of this disease.

INTRODUCTION

Many intrathoracic manifestations of rheumatoid disease have been recognized since Ellman and Ball described pulmonary fibrosis in association with rheumatoid arthritis in 1948, the most common being pleural effusion. Rheumatoid patients also have an increased incidence of non-specific acute and chronic bronchopulmonary infections (Walker 1967). Various pulmonary manifestations of the disease have been recognized, fibrosing alveolitis being the most frequent (Scadding 1960). Pulmonary rheumatoid nodules (Noonan et al. 1963) may be single or multiple, are usually in the peripheral lung fields and may cavitate. Caplan (1953) described the association of pulmonary rheumatoid nodules and pneumoconiosis in rheumatoid patients with coal-workers' pneumoconiosis. Rarer intrathoracic manifestations include pulmonary hypertension associated with pulmonary arterial intimal hypertrophy (Gardiner et al. 1957), acute pulmonary infiltration associated with pleuropericarditis (Beck & Hoffbrand 1966), and progressive airway obliteration (Geddes et al. 1977). A recent report (Macfarlane et al. 1978) described a patient with upper lobe fibrosis in association with rheumatoid disease.

We describe four patients with rheumatoid disease who were found to have upper lobe fibrosis and cavitation which were not related to pulmonary nodules or to any other recognized pulmonary manifestation of the disease.

Case Reports

Case 1

A retired coal miner developed rheumatoid arthritis at the age of 65. Cough and sputum developed three years later and a chest radiograph showed a right pleural effusion and bilateral upper zone fibrosis. He was given antituberculosis treatment for two years even though sputum was negative for tubercle bacilli and a tuberculin test was negative. One year after this treatment the radiograph showed extension of the upper lobe fibrosis with cavitation (Figs 1, 2).

Case 2

A housewife of 72 had had rheumatoid arthritis for 18 years and then developed cough, sputum and breathlessness. Chest radiograph showed fibrosis in both upper lobes with cavitation in the

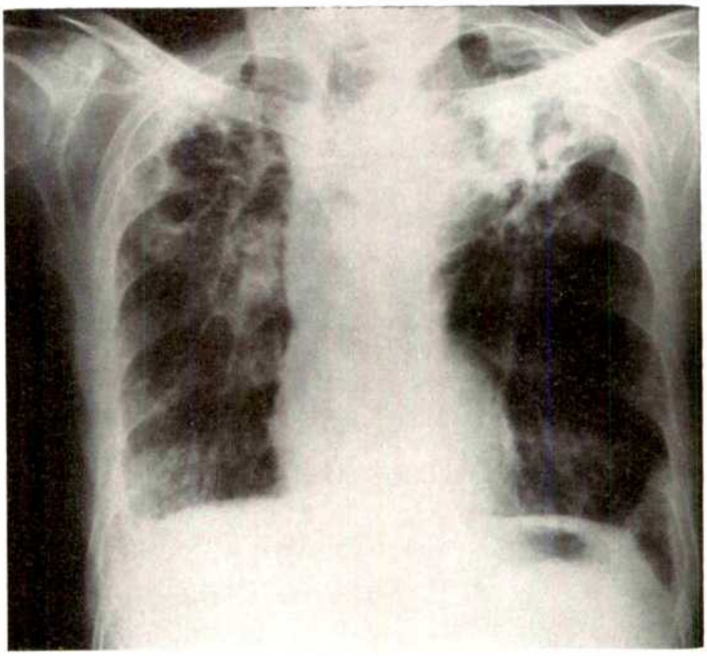

Fig. 1. Case 1. Bilateral upper lobe fibrosis and cavitation

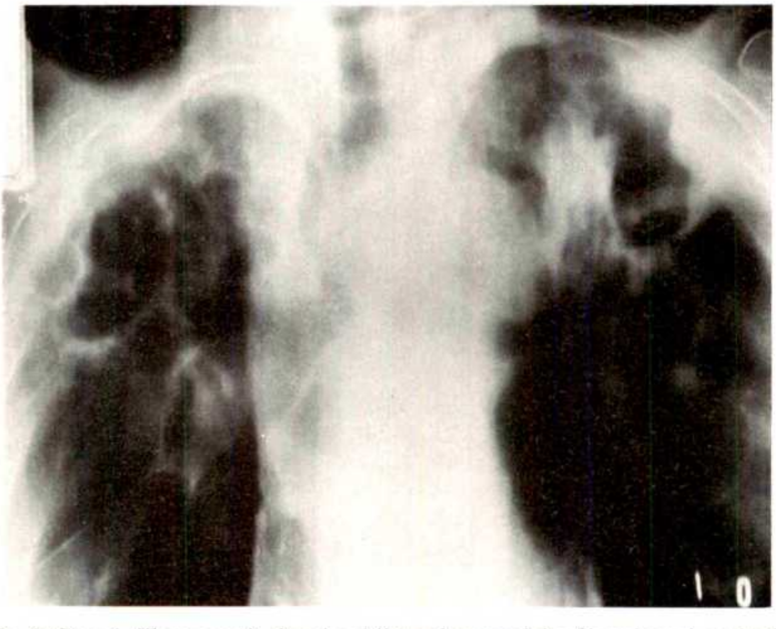

Fig. 2. Case 1. Tomograph showing bilateral upper lobe fibrosis and cavitation

right and also diffuse fibrosis in both lower zones. These features remained stable during one year of observation.

Case 3

A retired postal worker of 71 with a 15-year history of rheumatoid arthritis had cough and sputum for many years. His chest radiograph showed cavitation in both upper zones and changes suggestive of fibrosis in the left mid-zone which slowly progressed over a period of two years (Fig. 3).

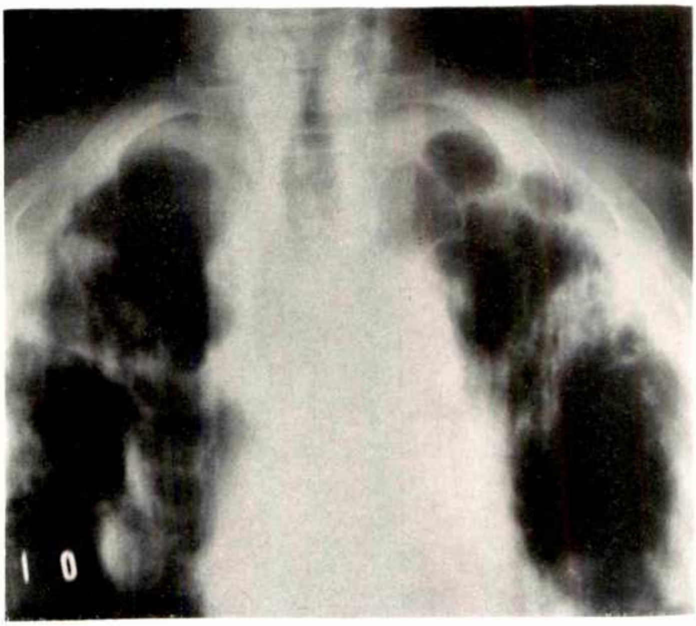

Fig. 3. Case 3. Tomograph showing bilateral upper lobe fibrosis and cavitation

Case 4

A 66-year-old retired warehouseman first developed rheumatoid arthritis at the age of 65. He had a life-long history of asthma of moderate severity and was known to have an abnormal chest radiograph at least ten years before the onset of arthritis. This radiograph showed predominantly right-sided upper lobe fibrosis and cavitation, an appearance which has changed little during continuous treatment with prednisolone in a daily dose of at least 7.5 mg (Fig. 4).

Investigations

In all patients repeated sputum examinations were negative for tubercle bacilli and *Aspergillus fumigatus*. All patients had negative skin prick tests to *A. fumigatus* and no serum precipitating antibodies to this fungus were demonstrated. There was no history of avian exposure. Sacroiliac joint radiographs were normal. The Kveim test was negative in the two patients in whom this investigation was performed (Cases 1 and 3). In all four patients rheumatoid factor was present in high titre, low levels of CH_{50} were also detected, and in two a low C_4 was found. One patient had a positive antinuclear factor and also circulating immune complexes (Table I)..

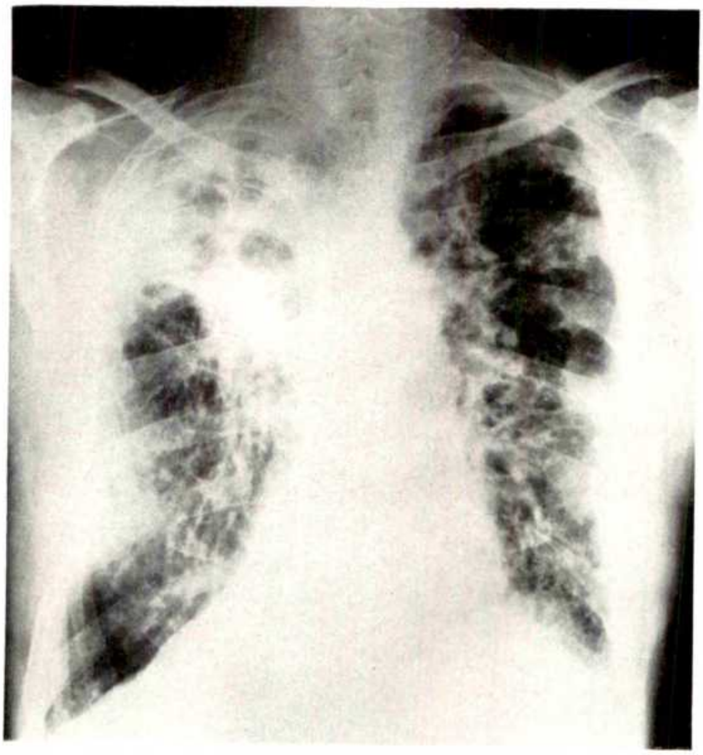

Fig. 4. Case 4. Bilateral pulmonary fibrosis with multiple cavities in the right upper lobe

Table 1. Laboratory investigations

Investigation	*Case 1*	*Case 2*	*Case 3*	*Case 4*
Rheumatoid factor titre	1/2048	1/4096	1/4096	1/1024
Antinuclear factor	Positive	Negative	Negative	Negative
Aspergillus precipitins	Negative	Negative	Negative	Negative
Sputum fungi	Negative	Negative	Negative	Negative
Sputum *M. tuberculosis*	Negative	Negative	Negative	Negative
Complement (CH_{50})	Reduced	Reduced	Reduced	Reduced

Treatment and progress

Because of the radiographic changes three patients were treated with prednisolone 20 mg daily. In two cases (Cases 2 and 3) the radiographic appearances did not alter. One of these (Case 2) died of an intercurrent pneumonia, but permission for autopsy was withheld. Another patient (Case 1) developed haemoptysis associated with the appearance of a solid lesion in the left upper lobe, which was subsequently found to be a squamous carcinoma. The apical fibrosis and cavitation preceded the carcinoma, and the right-sided changes were clearly unrelated to tumour.

The remaining patient (Case 4) had been treated for asthma with prednisolone in a dose of 7.5 mg daily for many years and little change in the fibrosis and cavitation was observed. In this patient there was no evidence to suggest asthmatic pulmonary eosinophilia as a cause of the radiographic changes.

DISCUSSION

Cavitated lung lesions in patients with rheumatoid disease are usually ascribed to the cavitation of pulmonary rheumatoid nodules. The four patients reported here had active rheumatoid disease and developed upper lobe fibrosis and cavitation which could not be explained by the cavitation of rheumatoid nodules.

With one exception (Case 4) no patient had previously been treated with corticosteroids, penicillamine or gold salts, but all had taken aspirin preparations for many years. The underlying pathology is not clear as percutaneous and transbronchial lung biopsy yielded only necrotic tissue. Open lung biopsy was not performed. Permission for autopsy was not obtained in either patient who died (Cases 1 and 2). In all patients, with the exception of the one who died from an intercurrent pneumonia, the disease followed a chronic course over a number of years.

In Case 4 the pulmonary changes preceded joint symptoms by years, and in all patients the lung changes were not obviously associated with exacerbations of joint symptoms. The rheumatoid factor was positive in high titre and there was laboratory evidence of circulating immune complexes. In simple rheumatoid arthritis measurements of serum complement are normal, but in the presence of vasculitis and circulating immune complexes changes in the pattern of serum complement occur. A low level of CH_{50} was seen in all patients, two of whom also had a low C_4 and in Case 3 serum complement returned to normal with prednisolone treatment. The apical changes reported here may be related to the intrapulmonary deposition of circulating immune complexes. However, these abnormalities may be non-specific since similar radiographic appearances are now recognized in ankylosing spondylitis (Davies 1972; Crompton et al. 1974). We suggest that non-nodular upper lobe cavitation and fibrosis may be added to the list of recognized intrathoracic manifestations of rheumatoid disease.

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COMPARISON OF FENOTEROL AND TERBUTALINE ADMINISTERED BY INTERMITTENT POSITIVE PRESSURE BREATHING

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Summary

The bronchodilator properties and side-effects of three doses of fenoterol (0.5 mg, 1 mg and 2 mg) and terbutaline (2.5 mg, 5 mg and 10 mg) were assessed in 12 patients with stable chronic asthma. The drugs were administered by intermittent positive pressure breathing (IPPB) in 40% oxygen via a Bennett ventilator. No differences likely to be of clinical significance were found between the effects of the three different dose levels of fenoterol and terbutaline, although terbutaline had a significantly greater duration of action. It is concluded that fenoterol 2 mg and terbutaline 10 mg can be administered by IPPB in 40% oxygen for the treatment of asthma.

Introduction

Since the introduction of orciprenaline, the first beta agonist with some selective beta_2 properties, a number of drugs with greater beta_2 specificity have become available and these include terbutaline, salbutamol, fenoterol and rimiterol. Rimiterol has a short duration of action because of its breakdown by catechol-*O*-methyl transferase (COMT) whereas the other drugs have a longer therapeutic effect because of their resistance to COMT. The bronchodilator properties of salbutamol and terbutaline are virtually identical (Paterson & Shenfield 1974), but it has been reported that fenoterol has a more prolonged duration of action (Petit & Roberts 1973).

This study was designed to compare the bronchodilator properties and side-effects of terbutaline and fenoterol when administered by intermittent positive-pressure breathing (IPPB) using a patient-triggered ventilator. The doses of terbutaline chosen were those recommended by Simmonson et al. (1976) (2.5 mg and 5 mg) plus a larger dose of 10 mg. Fenoterol has a higher weight-for-weight potency than terbutaline and the doses chosen were those recommended to us by the manufacturers (0.5 mg and 1 mg) plus a larger dose of 2 mg. Three dose levels of both drugs were used in an attempt to discover the optimal dose beyond which side-effects would be prohibitive.

Patients and Methods

Twelve patients with stable chronic asthma in whom a greater than 25% increase in forced expiratory volume in one second (FEV_1) was demonstrated following the administration of salbutamol by IPPB were chosen for the study. All had base-line FEV_1 values of less than 70% of the predicted normal. There were eight men and four women with a mean age of 51.8 years (range 24–73). All regularly used a bronchodilator aerosol; ten were being treated with an inhaled corticosteroid preparation and six of these were also taking a small dose of prednisolone. Haematological and biochemical indices were normal prior to entry.

The study was a double-blind comparison of terbutaline 2.5 mg, 5 mg and 10 mg and fenoterol 0.5 mg, 1 mg and 2 mg. The drugs were made up in volumes of 1.5 ml and administered by IPPB in 40% oxygen using a Bennett ventilator with standardized pressure settings and nebulizer rates.

On each morning base-line measurements of heart rate and blood pressure were made after a 30-minute rest. The FEV_1 and forced vital capacity (FVC) were then measured using a dry spirometer (Vitalograph), the best of three measurements being accepted. The maximum mid-expiratory flow (MMEF) was calculated from the spirometer trace. Peak expiratory flow rate (PEFR) was recorded using a Wright peak flow meter, the best of three being accepted. Ventilatory function measurements were repeated ten minutes later immediately prior to drug administration and at 5, 10, 20, 30, 60, 120, 180, 240 and 300 minutes after drug administration. Heart rate (Hewlett Packard Cardiac Monitor) and blood pressure were recorded at the same times and any side-effects spontaneously reported by patients were also recorded. If the pre-treatment FEV_1 varied by more than 15% from that recorded on the first day the test was abandoned and repeated on a subsequent day when there was less than 15% variation in FEV_1. The precautions reported by Paterson et al. (1977) were taken to avoid drug contamination of the nebulizer and ventilator tubing.

RESULTS

For each drug the effects of three dosages were compared. Comparisons were also made between the effects of the two drugs at each of three different dosages: i.e. terbutaline 10 mg *vs* fenoterol 2 mg, terbutaline 5 mg *vs* fenoterol 1 mg and terbutaline 2.5 mg *vs* fenoterol 0.5 mg. Statistical analyses were made by two way analyses of variance and paired *t*-tests.

Ventilatory function tests

FEV_1. The changes in FEV_1 are shown graphically in Fig. 1. Both drugs were rapidly

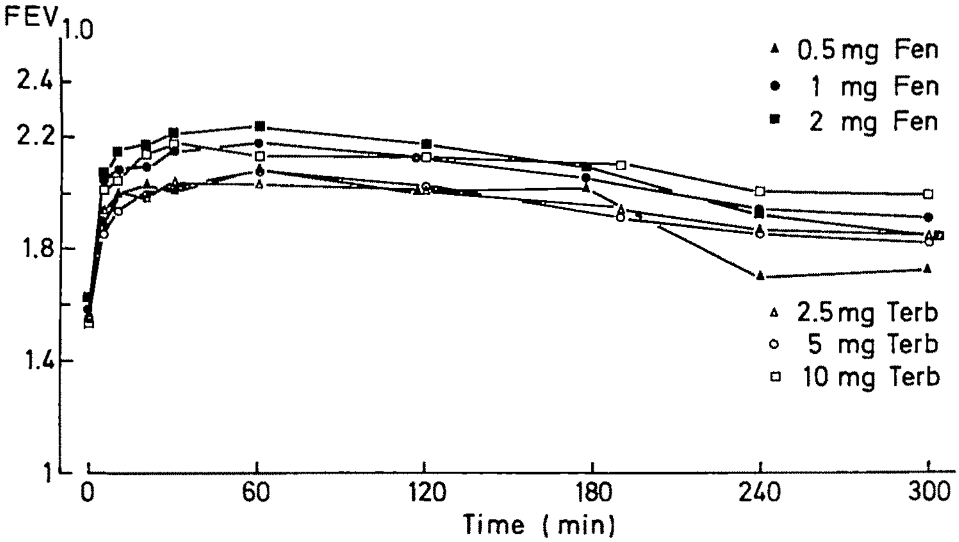

Fig. 1. FEV_1 response to various dosages of fenoterol and terbutaline

effective and the improvements in FEV_1 five minutes after drug administration were not significantly less than the peak effects for each drug. The greatest improvements in FEV_1 produced by fenoterol 2 mg and terbutaline 10 mg were not statistically different (39% and 42.5% respectively). At 300 minutes the improvement in FEV_1 produced by terbutaline 10 mg was statistically better than that following fenoterol 2 mg ($P < 0.001$). With both drugs the peak effects and duration of effect showed a tendency to increase with dosage, but these differences were not statistically significant.

FVC. The results are shown graphically in Fig. 2. The peak effects and duration of effect are similar to those of the FEV_1 responses but at 240 and 300 minutes the improvement produced by terbutaline 10 mg was significantly better than that following fenoterol 2 mg ($P < 0.05$).

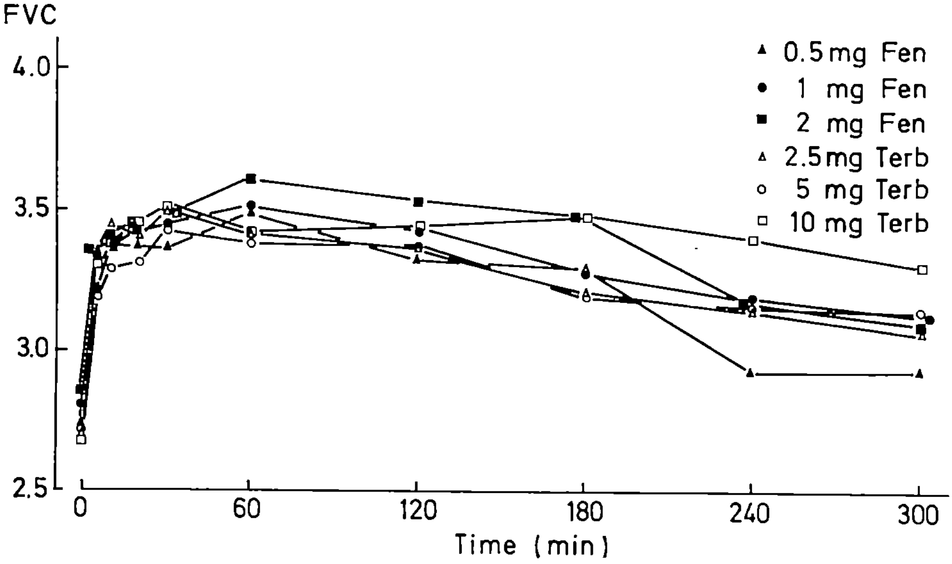

Fig. 2. FVC response to various dosages of fenoterol and terbutaline

MMEF and PEFR. The results are summarized in Table I. There were no significant differences between the effects of the different doses of fenoterol and terbutaline or in the between drug comparisons with regard to speed of action, peak effect or duration of action, although there was a tendency for higher doses of either drug to produce greater improvements.

Cardiovascular effects

Heart rate. A peak increase in mean heart rate of nine beats per minute was recorded after terbutaline 10 mg compared with a peak increase of mean heart rate of four beats per minute following fenoterol 2 mg. These changes are not significantly different from each other or from the base-line values.

Blood pressure. There were no significant changes in systolic or diastolic blood pressure following administration of the three dose levels of each drug.

Side effects. Tremor was reported by five patients after 2 mg of fenoterol and by three patients after 1 mg. Three patients reported tremor after 10 mg of terbutaline and one patient after 5 mg. Light headedness was reported by one patient after 10 mg of terbutaline and by one after 5 mg but did not occur after fenoterol.

Table I. Mean increases in MMEF and PEFR expressed as a percentage of pre-treatment value

Mean increase in	*Drug and dosage*	*Time after treatment (minutes)*				
		5	30	60	180	300
MMEF	Fenoterol 0.5 mg	11.9	21.3	24.5	16.5	0.7
	Fenoterol 1 mg	31.1	45.9	47.5	33.2	20.6
	Fenoterol 2 mg	37.7	57.0	56.0	22.0	12.4
	Terbutaline 2.5 mg	34.8	38.7	39.0	38.6	27.5
	Terbutaline 5 mg	23.4	42.9	42.0	24.5	19.7
	Terbutaline 10 mg	37.9	54.3	63.0	49.1	45.4
PEFR	Fenoterol 0.5 mg	20.2	34.5	36.3	27.8	11.2
	Fenoterol 1 mg	28.0	41.3	42.2	33.3	18.2
	Fenoterol 2 mg	31.0	46.5	50.1	31.0	23.5
	Terbutaline 25 mg	23.1	30.6	31.0	26.6	12.7
	Terbutaline 5 mg	26.7	37.3	40.1	29.0	27.6
	Terbutaline 10 mg	31.3	39.2	46.1	39.2	31.3

DISCUSSION

We have shown that fenoterol and terbutaline are effective bronchodilator drugs when given by IPPB. Both drugs were effective in the lowest doses used but peak and duration of effects tended to increase with higher doses. Fenoterol has been reported to have a longer duration of action than terbutaline (Petit & Roberts 1973) but our study failed to show any clinically significant differences between the drugs in this respect. Indeed terbutaline was found to have a statistically significant longer duration of action than fenoterol but this finding is unlikely to be of therapeutic significance. It is possible that the dose levels used in this comparative study are not equipotent since the mean increase in heart rate following terbutaline 10 mg was somewhat higher than that after fenoterol 2 mg. On the other hand there were more complaints of tremor after fenoterol than after terbutaline. Since all patients studied had been regularly treated with salbutamol for prolonged periods prior to the investigation it is probable that some degree of tachyphylaxis of side effects had developed (Svedmyr et al. 1976) and that greater increases in heart rate and more complaints of tremor would have been observed in patients who had not previously been treated with beta stimulant drugs.

The results of this study suggest that fenoterol and terbutaline are equally effective bronchodilator drugs with similar side effects and that fenoterol 2 mg and terbutaline 10 mg can be administered by IPPB in the treatment of asthma.

ACKNOWLEDGEMENTS

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BRONCHOALVEOLAR LAVAGE FOR THE PREPARATION OF FREE LUNG CELLS: TECHNIQUE AND COMPLICATIONS

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Summary

Bronchoalveolar lavage at fibreoptic bronchoscopy enables the peripheral bronchoalveolar free cell population, which consists mainly of lymphocytes and macrophages, to be sampled. The yield is sufficient for detailed morphological and functional investigation of these cells, which can be separated by exploiting the glass-adherent or phagocytic properties of macrophages. Such studies are of particular interest in patients with recurrent chest infections, to detect abnormalities of local cellular immunity; in pulmonary fibrosis to assess activity of the disease and effect of treatment by observing morphology and testing function of free lung cells; and in bronchial carcinoma to investigate local immune responses to the tumour. The procedure is held to be ethical in these circumstances. The lavage consists of irrigation of a segmental bronchus through the fibreoptic bronchoscope with up to 500 ml pH-corrected normal saline solution. It is contraindicated in those with respiratory or cardiac risk, but is tolerated well by most patients. Complications include acute respiratory distress, vasovagal syncope and fever with pulmonary infiltrates. Lavage is associated with a mean fall of $Pa{O_2}$ of 3.0 kPa (22.7 mmHg) and routine oxygen supplementation is recommended.

INTRODUCTION

Research into the immunology and cell biology of pulmonary disease has hitherto relied upon experiments using cells from the peripheral blood or from tissue obtained from open lung biopsy or autopsy. Blood cells are remote from the lung and the properties of tissue cells may be altered by the mechanical and enzymatic techniques needed to release them. The peripheral bronchoalveolar free cell population can now be sampled by bronchoalveolar lavage at fibreoptic bronchoscopy. The cells obtained include macrophages, lymphocytes, neutrophils, eosinophils and some mast cells and epithelial cells. The mononuclear cell yield is sufficient for study of their morphological and functional characteristics in disease states.

This paper describes the technique employed to harvest free lung cells and the clinical problems encountered, the laboratory technique used to prepare such cells for experiments and the technical problems encountered. Previous reports (Harris et al. 1970; Warr & Russell Martin 1974; Yeager et al. 1974) have described experience gained from small series of healthy persons and patients with non-infective disease or from a larger series of healthy persons (Reynolds et al. 1977). This report is based on a study of 120 subjects with recurrent acute respiratory infections, fibrosing alveolitis or carcinoma of the bronchus whose pulmonary cells were used in various functional tests.

ETHICAL CONSIDERATIONS

At Brompton Hospital the technique was first used for investigation of local pulmonary host defences of patients attending a clinic for study of chronic pulmonary infection. Such patients were initially screened for peripheral blood immunity defects; if none was found the patients gave informed consent to the procedure of bronchoalveolar lavage so that functional tests of free lung cell could be carried out *in vitro*. This procedure was held to be ethical because these patients were suffering from a condition serious enough to cause them distress, morbidity and often financial hardship due to loss of work and where, in the absence of a systemic immunity defect, a local lung defence defect might be present. Identification of such a defect would help attempts to devise individual treatment. Thus, there was a real possibility that the result of the test might favourably influence the patient's treatment, as well as furthering knowledge about the local immunity of the disease.

The ethical justification for the procedure in fibrosing alveolitis was the hope that information of potential value in the management of the individual patient would be obtained. The main problem in this disease is to detect and measure activity of the pathological process with and without treatment. Radiological and physiological criteria are often too insensitive to be clinically helpful, whereas morphological examination of free lung cells (rather than serial open-lung biopsies) might detect small changes in the inflammatory or fibrotic process which could influence treatment.

In treatment of carcinoma of the bronchus the host response of the patient to the tumour has rarely been considered. Variation in cytotoxic capacity of local mononuclear cells might conceivably explain observed variations in response to treatment where tumour histology and staging are identical. We believe that study of the local immunity in such patients may ultimately help to identify patients whose host response can be stimulated to allow standard treatment the greatest chance of success.

Methods

Bronchoalveolar lavage

Routine fibreoptic bronchoscopy was performed under local anaesthesia by the transnasal route. The patients were premedicated with omnopon 10–15 mg and atropine 0.6 mg and were given oxygen by nasal catheter throughout the bronchoscopy. After inspection of the bronchial tree biopsy specimens were obtained where indicated and lavage was then carried out in the other lung. The tip of the bronchoscope was impacted, usually in a segmental or more peripheral bronchus in the lateral or posterior segment of the lower lobe, and was held in place with gentle pressure by an assistant. Using a hand-held syringe, 60 ml of sterile 0.9% sodium chloride solution corrected to pH 7.0 was injected while the patient inhaled very slowly to total lung capacity and then quietly exhaled to functional residual capacity. Injections were repeated until 120–180 ml had been inserted. The tip of the bronchoscope was then withdrawn 1–2 cm and the fluid aspirated while the patient breathed quietly within the tidal range. The procedure was repeated until about 100–150 ml of fluid had been recovered, which usually entailed the insertion of a total of 300–500 ml of saline.

Contraindications

The procedure was considered to be contraindicated under the following circumstances:

1. 'Respiratory risk', defined as:
   a. Severe ventilatory defect (FEV_1 < 1.0 litres).
   b. Hypoxaemia at rest (Pa_{O_2} < 70 mmHg = 9.3 kPa).
2. 'Cardiac risk', defined as:
   a. Myocardial infarction within the previous six months.
   b. Unstable angina pectoris.
   c. Left or right ventricular failure.

Effect on pulmonary gas exchange

Six consecutive patients were investigated with serial arterial blood gas estimations during and after lavage. One had recurrent chest infections, two had pulmonary fibrosis and three had carcinoma of the bronchus. A base-line sample was drawn from a radial artery catheter before the bronchoscope was passed into the nose. Further samples were collected after lavage was completed and the bronchoscope removed and after 30 and 120 minutes. The samples were stored on ice and analysed within 30 minutes using a Corning EEL model 165 blood gas analyser.

Patient acceptability

A formal study of acceptability was made on 30 consecutive patients. The bronchoscopy procedure was explained and the patients told that at the end of the procedure a small part of the lung would be washed with fluid, and that this would be aspirated. The possibility of unpleasant choking sensations and coughing was stressed. Following the procedure, and on the same day, the patients were asked to mark a ten-point scale. Zero was marked 'horrible' and it was suggested that this meant that the procedure was totally unacceptable and would not be consented to in the future under any circumstances. The mid point was marked 'as expected'. The top point was marked 'quite acceptable' and it was suggested that this be compared with having a dental inspection.

Morbidity

Complications following the procedure were recorded. Forty-two patients were studied prospectively with a four-hourly record of temperature and a chest radiograph at 24 hours.

Laboratory preparation of cells

Pulmonary lavage fluid is collected in siliconized 'trap' containers on ice and taken immediately to the laboratory where it is strained through cotton gauze to remove mucus and centrifuged at 200 *g* for 10 minutes at 4°C. Supernatant fluid is removed and stored at −80°C, while the cell pellet is resuspended in medium 199 in the presence of 5% human serum. A differential viable cell count is performed before and after incubation of the counting chamber at 37°C in an atmosphere of 5% CO_2 in air. A cytocentrifuged, Giemsa-stained permanent preparation is made of the cell suspension for subsequent reference.

The cells obtained are mainly mononuclear (lymphocytes and macrophages) which can be separated by one of a variety of techniques depending on the cell type to be studied. Macrophage cultures can be prepared by adding 1 ml aliquots of cell suspension in medium-serum to glass coverslips during an incubation period of 30 minutes at 37°C in an atmosphere of 5% CO_2 in air. Non-adherent cells, mainly lymphocytes, can be washed away vigorously leaving a culture of macrophages which are 98% pure as judged by phagocytic tests. Lymphocyte-rich cell suspensions can be obtained by removing macrophages using their property of glass-adherence or phagocytosis (magnetic removal of cells which have ingested carbonyl iron).

The major technical problem encountered in these procedures is contamination with red blood cells, mucus and neutrophils (or pus). Heavy contamination is usually overcome by centrifuging the cell suspension on a Ficoll-Triosil density gradient and harvesting mononuclear cells which band at the interface of the medium and the Ficoll-Triosil. Problems encountered thereafter are usually due to fungal contamination, presumably introduced from the pharynx during passage of the bronchoscope. Fungus growth appears several hours after the preparation of the cell cultures and is prevented by addition of antifungal agents to the lavage fluid as soon as it is collected from the lung. The majority of bacterial phagocytosis and killing assays are complete within two or three hours of the lavage procedure, obviating the requirement for antibacterial or antifungal agents to control contamination, but this remains a problem in cultures required for longer experiments.

RESULTS

Cell yields. There was considerable variation with disease and smoking habits. Twenty-five non-smokers with recurrent acute respiratory infection studied between attacks yielded between 3 and 36×10^6 cells (mean 21×10^6). The percentage of macrophages

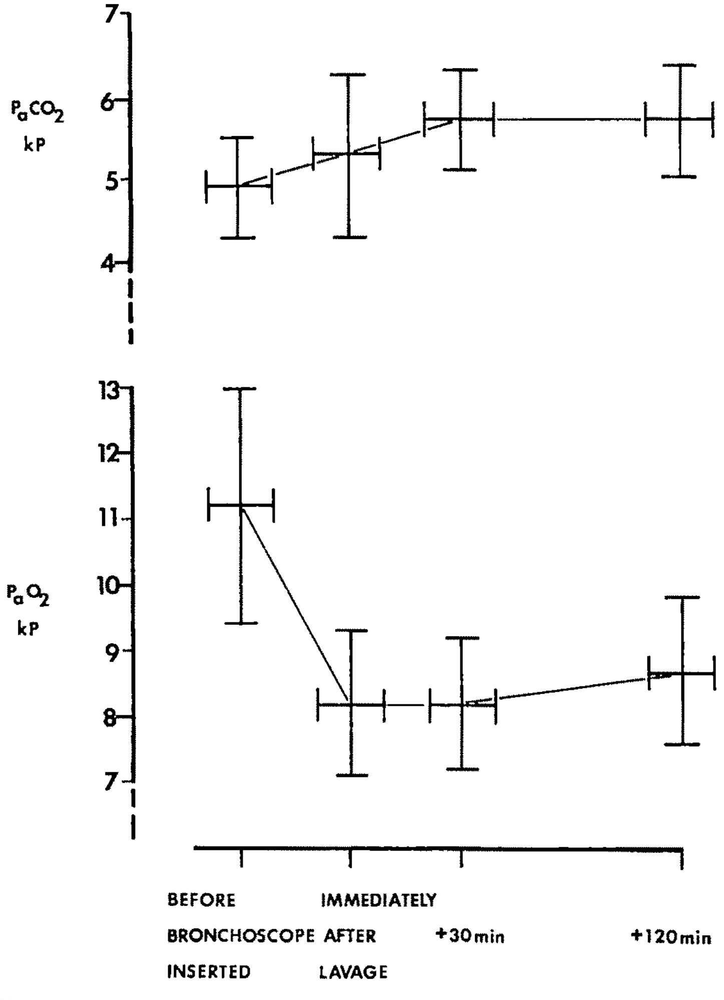

Fig. 1. Arterial blood gases during bronchoalveolar lavage in six patients

varied from 54 to 96%. Details of differential cell counts according to smoking habit, disease and treatment will be the subject of later reports.

Arterial blood gases. The results of $P\text{aco}_2$ and $P\text{ao}_2$ during and following lavage of six patients are shown in Fig. 1. There was no significant change in $P\text{aco}_2$ which remained within normal limits. The initial mean $P\text{ao}_2$ was 11.2 kPa (84.0 mmHg), which fell following lavage by a mean of 3.0 kPa (22.7 mmHg) to 8.2 kPa (61.2 mmHg). The lowest $P\text{ao}_2$ recorded was 6.5 kPa (49.0 mmHg). $P\text{ao}_2$ remained reduced 120 minutes after completion of lavage.

Patient acceptability. The mean acceptability score in 30 consecutive patients was 5.3 and only two (6.7%) found the experience unacceptable.

Morbidity. The following complications were encountered:

1. *Respiratory distress.* The lavage procedure was terminated prematurely in three patients out of 120 because of acute respiratory distress. This lasted only a minute after removal of the fibreoptic bronchoscope.
2. *Syncope.* Three of 120 patients developed pallor, loss of consciousness, profound bradycardia and hypotension during or immediately following the procedure. Recovery was rapid after removal of the bronchoscope and lying the patient flat, but one patient required 2.4 mg atropine intravenously. These events occurred despite administration of 0.6 mg atropine in the premedication. One other patient developed a similar vasovagal episode during bronchoscopy but before lavage. These patients appeared to be resistant to atropine.
3. *Fever and radiographic pulmonary shadowing.* Eight of 42 patients developed fever and six of these had radiographic shadowing. Five of the fevers and four of the shadowings were in patients with frequent infection syndrome. These complications rapidly cleared with antibiotics and physiotherapy.

CONCLUSION

Bronchoalveolar lavage appears to be an acceptable addition to fibreoptic bronchoscopy in terms of time, discomfort to the patient and morbidity. The maintenance of $P\text{aco}_2$ suggests that alveolar ventilation is not impaired by lavage. The significant fall in $P\text{ao}_2$ is probably related to continued perfusion of lung which is abnormally ventilated following lavage, resulting in 'shunting' of poorly oxygenated blood. Similar changes occur, but probably less frequently, during fibreoptic bronchoscopy without lavage. We recommend that oxygen should be given routinely to patients during and after lavage, and practice at Brompton Hospital is to give 2 litres per minute by nasal specula.

The procedure allows the collection of large numbers of free peripheral bronchoalveolar cells which has not been possible previously. Study of the structure and function of these cells may increase understanding of disease processes and may have implications in the management of various clinical problems. The components of the lavage supernatant can be studied qualitatively, but the variable degree of dilution makes accurate quantitation difficult and this problem has yet to be overcome. The results of studies on patients with recurrent respiratory infection, fibrosing alveolitis and bronchial carcinoma will be the subjects of further reports.

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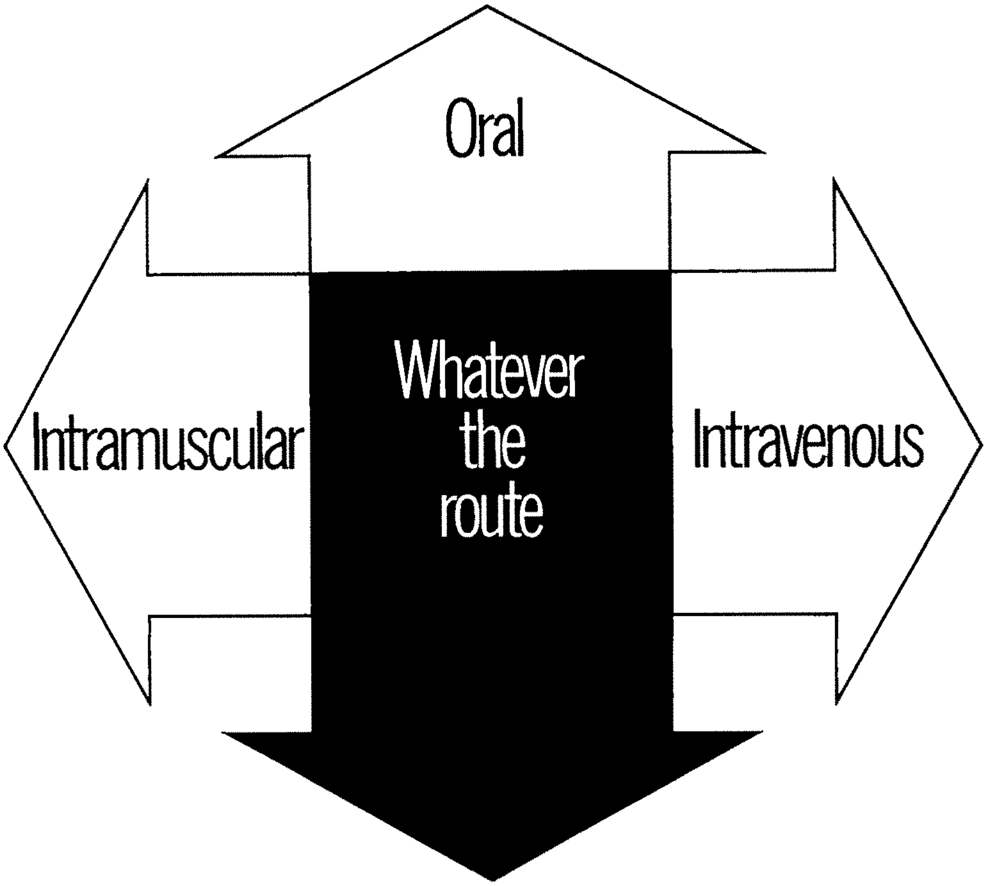

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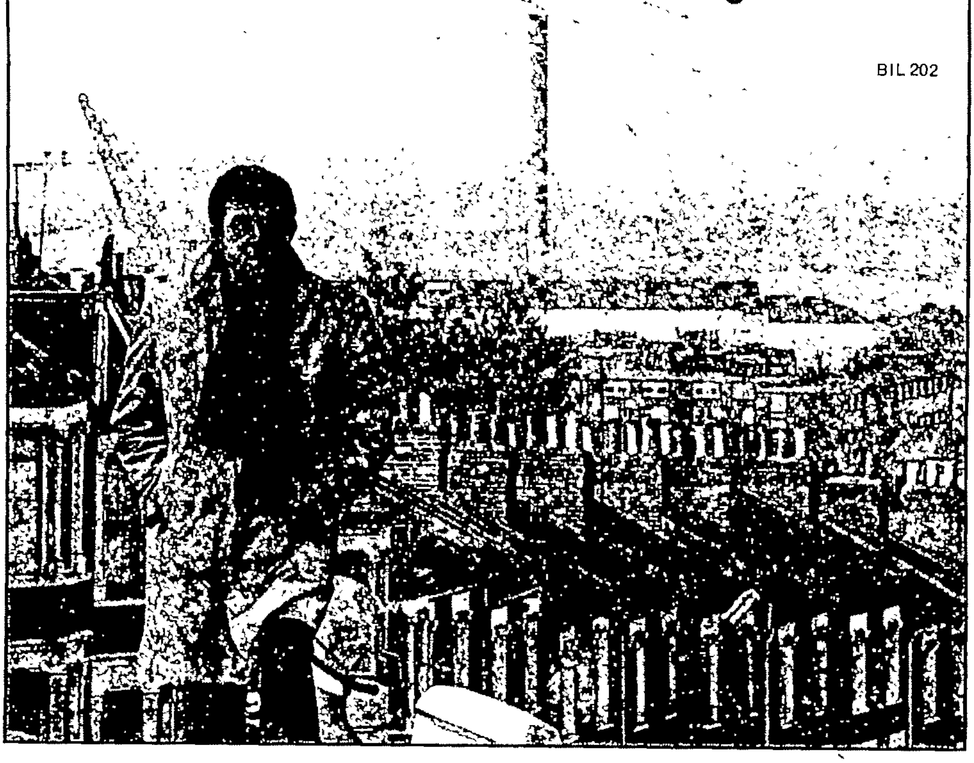

Br. J. Dis. Chest (1980) 74, 279

CIGARETTE SMOKING IN ASTHMA

T. W. Higenbottam, C. Feyerabend and T. J. H. Clark

Guy's Hospital, London

Summary

A survey was performed of smoking habits and respiratory symptoms of 106 asthmatic patients attending a hospital out-patient clinic. A quarter of the patients were currently smokers and a further quarter were ex-smokers. Less than a third of the smokers complained of symptoms of wheeze or dyspnoea after smoking. Asthmatic smokers had a much higher prevalence of chronic cough but their lung function appeared no lower than non-smokers.

Ten asthmatic smokers were selected to contrast their acute bronchial response to smoking a currently marketed cigarette with that of ten asymptomatic smokers. Only four of ten asthmatic patients and two of ten asymptomatic smokers developed acute airway narrowing after smoking despite changes in venous blood nicotine levels which confirmed cigarette smoke inhalation.

Many more asthmatic patients smoke than might be expected from the known instability of their airways. Our failure to show frequent and substantial airway reactivity to cigarette smoke in these patients suggests either that cigarette smoke may not be as acutely irritant as might be anticipated or that some asthmatic patients acquire tolerance to it. The effects of chronic cigarette consumption could be demonstrated even in this small sample which suggests that asthmatic patients should be advised to stop smoking, especially as many clinicians expect asthma and smoking to be a rare coincidence.

INTRODUCTION

Inhalation of cigarette smoke is thought to irritate airways. This irritation may be responsible for mucus hypersecretion (Fletcher et al. 1976) and is also thought to explain changes in airway function previously observed in some normal individuals (Nadel & Comroe 1961; Guyatt et al. 1970) and asthmatic patients (Gayrard et al. 1974), in whom smoking a cigarette appeared to cause acute airway narrowing.

Asthmatic patients are well known to have marked bronchial hyper-reactivity (Itkin 1967) and, in view of this, it might be expected that they would be unlikely to smoke cigarettes. Our clinical experience did not support this view and we have, therefore, set out to examine smoking habits of asthmatic patients and, as a corollary, to study the acute effects of inhaled tobacco smoke in asthmatic patients who habitually smoke cigarettes.

Methods

One hundred and six consecutive patients attending asthma clinics were interviewed. Each had demonstrated greater than 15% changes in peak expiratory flow rate (PEFR) either spontaneously or with treatment. Skin testing revealed that 70 were positive to at least two common allergens.

Under supervision each patient completed an MRC questionnaire on respiratory symptoms (Medical Research Council 1966), which included additional questions on symptoms of breathlessness or wheezing after smoking a cigarette or after entering a (cigarette) smoky environment. Three measurements of PEFR were made and the highest recorded.

A small group of habitual smokers was studied to determine the acute response to smoking. They included ten asthmatic smokers selected at random from the survey patients (six men and four women with a mean age of 35 years), none of whom was on steroid therapy. Contrasted with them was a group of ten normal male smokers with a mean age of 30 years. Each was asked to smoke in a usual manner a single low–middle tar filtered cigarette (1.36 mg nicotine per cigarette; Department of Health and Social Security 1976) having foregone cigarettes for at least 90 minutes before this study. The asthmatic patients had not used bronchodilator therapy for 24 hours.

Six measurements of inspiratory airway resistance and lung volume were determined in rapid succession before and within three minutes after smoking using a whole body box plethysmograph (Dubois et al. 1956). Venous blood was drawn before and two minutes after finishing, the cigarette for measurement of the level of nicotine (Feyeraband et al. 1965) to provide an assessment of the amount of smoke inhaled.

Using the whole survey population as a reference the prevalence rates of respiratory symptoms in non-smokers, smokers and ex-smokers were standardized for age (Armitage 1971). The PEFR recordings were converted to a percentage of predicted value for each patient (Cotes 1975).

In the acute cigarette provocation study measurements of airways resistance and lung volume were submitted to analysis of variance; mean values before and after smoking were contrasted using a multiple comparison technique to provide a test for significance; multiple t-ratios (Kirk 1968) (P values of 0.05 for each comparison).

RESULTS

About a quarter of the asthmatic patients were smokers and another quarter were ex-smokers (Table I).

Table I. Number of asthmatic subjects in each age group together with their smoking habit, average daily cigarette consumption (for smokers) and number of years of smoking

Age group	*Non-smokers*	*Ex-smokers*	*Smokers* (average number daily cigarettes; years smoking)
≤30	15	4	7 (24; 8 years)
30–39	9	8	6 (14; 15 years)
40–49	13	1	3 (5; 24 years)
50–59	9	9	7 (16; 38 years)
>60	6	5	4 (10; 45 years)
Percentage of total	49	25.5	25.5

The prevalence of respiratory symptoms (age adjusted) as assessed from the questionnaire is shown in Table II. A regular cough was reported more commonly amongst smokers, but acute respiratory episodes occurred at similar rates in all groups. All the groups reported a high frequency of wheezing or whistling but fewer smokers than non-smokers and ex-smokers reported breathlessness on exercise. Concerning reported acute effects of smoking, 37% of smokers and 16% of ex-smokers described breathlessness or wheezing after a single cigarette, whereas a smoky atmosphere produced these symptoms most commonly amongst ex-smokers.

Table II. Percentage of subjects with respiratory symptoms

Symptoms (MRC question no.)*	*Non-smokers* ($n=52$)	*Ex-smokers* ($n=27$)	*Smokers* ($n=27$)
Chronic cough (6)	42	49	73
Chronic cough and phlegm (10)	25	37	51
Acute cough and phlegm (12)	44	32	54
Breathlessness only (14)	48	57	40
Wheezing only (15)	85	92	93
Wheezing and breathlessness after a cigarette	0	16	37
Wheezing and breathlessness in a smoky atmosphere	50	64	45

*Medical Research Council (1966).

Results of respiratory function as assessed by the percentage of predicted value or PEFR revealed no significant difference between the groups (non-smokers 81.9% SE ±22.2, ex-smokers 73.4% SE ±27.7, smokers 69.9% SE ±33.4).

The acute effects of smoking in both asthmatic patients and normal subjects are shown in Fig. 1. In four asthmatic smokers and two normal smokers there was a significant rise in airways resistance ($P>0.05$), smoking having no significant effect upon lung volume, but two subjects in both groups showed bronchodilatation after smoking. All the volunteers inhaled cigarette smoke as judged by change in the level of venous blood nicotine, although there was no relationship between the changes in airway resistance and blood nicotine level (Fig. 2).

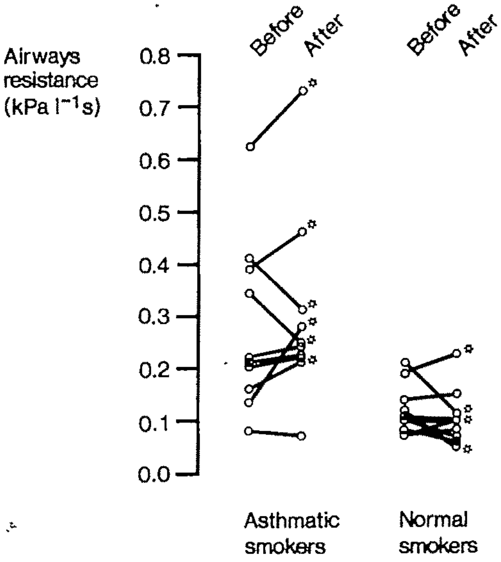

Fig. 1. Airway resistance before and after smoking in ten asthmatics and ten normal smokers. The asterisks indicate a statistically significant change ($P<0.05$)

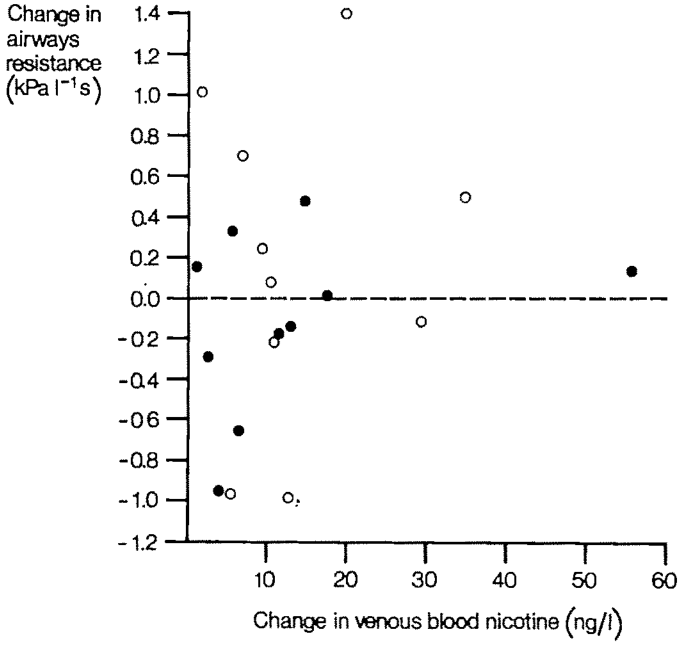

Fig. 2. The relationship between change in airway resistance after smoking and change in level of venous blood nicotine. The symbol ○ represents asthmatic and symbol ● normal smokers

DISCUSSION

Despite the likelihood that our asthmatic patients have highly reactive airways, airway resistance was significantly increased after smoking in only four of ten asthmatic patients compared with two of ten non-asthmatic smokers whilst two asthmatic patients and two normal smokers responded with bronchodilatation. This lack of a consistent effect is in accord with our other observation that a surprisingly high proportion of asthmatic patients smoke cigarettes and may explain the low frequency of reported symptoms after smoking. These findings suggest that inhaled tobacco smoke may not be as irritant to airways as previously supposed. A more narrow interpretation of our observations could be that inhaled smoke does not always excite irritant receptor activity. Clearly this conclusion does not exclude other effects of chronic tobacco smoke inhalation such as mucus hypersecretion and chronic damage to airway walls; this study of asthmatic smokers provides some evidence for this in that the prevalence of a regular cough was increased in smokers but, on the other hand, the smokers did not have a lower mean PEFR than non-smokers.

We have not excluded the possibility that cigarette smoking asthmatics may become conditioned so that bronchial reactivity declines, allowing habitual smokers to accept and tolerate the putative irritant effects of cigarette smoke. However, in a separate study we were unable to detect a significant difference in the degree of bronchial reactivity, as measured by histamine, between groups of habitual smokers and non-smokers (Higenbottam et al. 1978).

A more probable explanation is that smokers, be they asthmatic or normal, adopt a manner of inhalation of cigarette smoke which avoids or minimizes its irritant nature. There is some evidence for this, in that direct smoke inhalation in habitual smokers resulted in acute bronchoconstriction whereas the usual pattern of smoking which involves holding the smoke in the mouth before inhaling (Rawbone et al. 1978) failed to produce such acute airway narrowing (Higenbottam et al. 1980).

The cigarettes chosen for airway challenge come from those currently marketed and it should be remembered that tar content of cigarettes has fallen considerably over the past decade (Todd 1975). A further possibility therefore, is that the irritant effects of cigarettes previously described (Nadel & Comroe 1961; Guyatt et al. 1970) were the result of their relatively greater tar delivery and irritant quality.

In conclusion, our results suggest that tobacco smoke may not be as acutely irritant to the bronchial tree as was previously thought. A distinction needs to be drawn between the potential acute effects of cigarette smoking and the long-term effects on airway structure and function produced by chronic consumption of cigarettes. On the basis of some evidence of enhancement of these latter effects in asthmatics, it would seem wise to advise such patients against smoking. The relationship between acute effects and the possibility of chronic damage to airways requires further explanation.

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MODIFICATION TO THE TECHNIQUE OF PERCUTANEOUS PLEURAL BIOPSY USING ABRAMS' NEEDLE

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INTRODUCTION

The importance of obtaining a specimen of pleura for diagnosis in pleural effusions is established. It is technically difficult, however, to obtain adequate specimens consistently and success rates of about 70% are generally reported in previous studies (Heller 1956; Donohoe et al. 1957; Kettel & Cuggell 1967; Hyde et al. 1973; Reif 1974; Hoff & Li Volsi 1975; Emerson 1976). In most published studies the clinicians performing the biopsies had considerable skill and experience. We report a simple manoeuvre by which parietal pleura is sucked into the orifice of the biopsy needle and we believe that this technique may improve the yield of biopsies.

Method

1. The chest wall is cleaned and prepared in the usual manner and skin and subcutaneous tissue are infiltrated with local anaesthetic. An incision is made through skin and subcutaneous tissues using a No. 11 scalpel blade.
2. The Abrams' needle with the cutting aperture closed is advanced carefully through the incision. The aperture is opened and samples of fluid collected for routine examination.
3. The instrument is slowly withdrawn while slight traction is applied to the plunger of the 50 ml glass syringe until the point is reached where fluid is no longer aspirated.
4. The apparatus is advanced again about 1 cm into the effusion and is then tilted laterally through 90° until the syringe and needle lie parallel to the ribs. The knob on the collar of the Abrams' needle should be pointing towards the operator, indicating that the orifice is now facing the parietal pleura.
5. The collar of the Abrams' needle is held firmly between the thumb and index finger of the left hand with the barrel of the syringe lying loosely in the palm. With traction applied to the plunger the apparatus is tilted laterally until fluid can no longer be aspirated. The orifice is now lying against the parietal pleura.
6. Traction is maintained on the plunger to draw parietal pleura into the orifice and the biopsy is completed by twisting the syringe to advance the cutting edge.
7. The apparatus is returned medially through 90° and advanced about 1 cm to tear off the biopsy specimen if this has not been completely severed by the cutting edge. On removal of the needle a delicate filament may be seen trailing from the edge of the closed aperture and the main biopsy will be revealed by opening the aperture of the Abrams' needle.

RESULTS

We have used this method of obtaining pleura in 38 patients to date and have achieved success in 37 patients. Four junior doctors, who had never before attempted pleural biopsy, used the procedure and collected a good specimen on each occasion. We hope that this modification to the commonly used technique will improve the diagnostic yield of percutaneous pleural biopsy.

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DIAGNOSIS OF *NOCARDIA* PNEUMONIA BY TRANSTRACHEAL ASPIRATION

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Summary

We report a case of pulmonary nocardiosis in which the microbiological diagnosis was made by transtracheal aspiration after all conventional methods had failed. The simplicity of the technique and the importance of diagnosing nocardiosis are discussed.

INTRODUCTION

Nocardiosis is an uncommon cause of pneumonia and empyema, usually in immunosuppressed individuals. Transtracheal aspiration is frequently employed in the USA for unexplained pneumonia, but is seldom performed in the UK. The technique enables an accurate diagnosis to be made without contamination from upper respiratory tract organisms. We report what we believe to be the first case in which transtracheal aspiration enabled *Nocardia asteroides* to be cultured when all conventional methods had failed.

Case Report

A 23-year-old Jamaican housewife presented with thrombocytopenia in 1963 and underwent splenectomy. However, she developed proteinuria in 1967 and a renal biopsy confirmed systemic lupus erythematosus. Despite treatment with prednisone, her renal function deteriorated and she started regular haemodialysis in 1972. In 1973, she required a parathyroidectomy and shortly afterwards she received a renal transplant which functioned satisfactorily. She remained immunosuppressed on azathioprine and prednisolone from 1973, hypertension and diabetes being adequately controlled with hypotensive drugs and chlorpropamide. In March 1979 she developed a widespread vesicular rash, with haemoptysis and extensive nodular shadowing in both lungs. Electron microscopy of vesicle fluid demonstrated herpesvirus-like particles, later identified as *Herpesvirus varicellae*. Varicella pneumonia was diagnosed and she was treated with hyperimmune gammaglobulin and adenine arabinoside. She made a complete recovery despite a temporary increase in blood urea.

Six weeks later, she was re-admitted with pleuritic chest pain, intermittent fever, night sweats and progressively increasing coarse nodular shadowing in her right lower zone.

Several suprapubic skin ulcers appeared from which herpes simplex virus was cultured. She could produce no sputum and four blood cultures were negative. *Bacteroides fragilis* was cultured from her ulcers and she was treated with flucloxacillin, benzylpenicillin and metronidazole. She continued to deteriorate despite the addition of rifampicin and isoniazid. Transtracheal aspiration with a 17-gauge Bardicath inserted through the cricothyroid membrane produced 2 ml of aspirate. Direct microscopy revealed no significant findings. Unfortunately, she died before *Nocardia asteroides* was grown from the specimen. Autopsy showed a purulent infection of her right lower lobe with a small right empyema. The pus contained organisms which grew aerobically and formed branching hyphae characteristic of *Nocardia asteroides*. There was no evidence of graft rejection and no other autopsy findings which appeared to contribute to her death.

DISCUSSION

Nocardia asteroides is an aerobic, filamentous, acid-fast organism which is not a normal commensal in the respiratory tract of man. (Raich et al. 1960). It is usually identified by culture of sputum, empyema fluid or blood. In this patient, blood cultures were repeatedly sterile and the patient could not expectorate sputum. She presented the problem of a severely immunosuppressed patient with a worsening pneumonia. *Staphylococcus aureus* or *Bacteroides fragilis* was thought to be the most likely pathogen, but she did not respond to the appropriate antibiotics or to the addition of antituberculous drugs.

The technique of transtracheal aspiration is simple and has been well described (Pecora 1963; Kalinske et al. 1967; Hahn & Beaty 1970). If aspiration of bronchial secretion is difficult, the instillation of a few millilitres of normal saline almost invariably produces a satisfactory specimen. This procedure has the advantage over fibreoptic bronchoscopy in that the samples obtained are uncontaminated by upper respiratory tract flora. This is particularly important when anaerobic and opportunistic organisms are suspected. Complications such as haemorrhage around the puncture site and subcutaneous emphysema are rare.

There has been only one, poorly documented, previous report (Deresinski & Stevens 1974) of growth of *Nocardia* species using this method, but the present case shows that it may provide the diagnosis when sputum and blood cultures do not. The microbiological diagnosis of nocardiosis is essential because it usually responds well to appropriate antimicrobial chemotherapy. Frazier et al. (1975) cite various antibiotic regimens including trimethoprim and sulphamethoxazole, cycloserine and sulphonamides, erythromycin, ampicillin and minocycline. They suggest that the treatment of choice is now trimethoprim and sulphamethoxazole with a minimum of two to three months effective treatment. Unless nocardiosis is considered in the differential diagnosis and the organism cultured, the correct treatment will be instituted only by chance and is unlikely to be continued long enough to eradicate the infection.

We suggest that transtracheal aspiration should be more widely used when opportunist infections are suspected, especially if expectoration of sputum is difficult, and emphasize the importance of considering *Nocardia* in particular as a cause of pneumonia in immunosuppressed patients.

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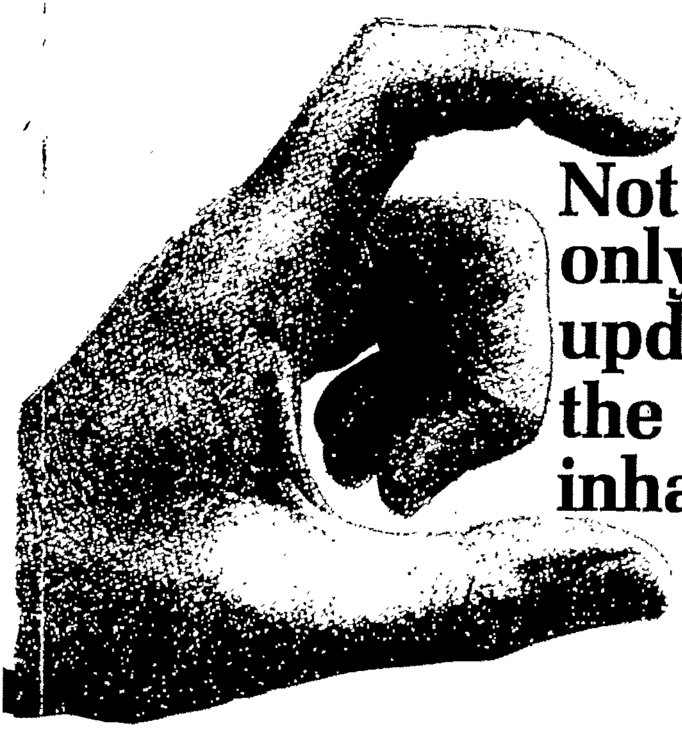

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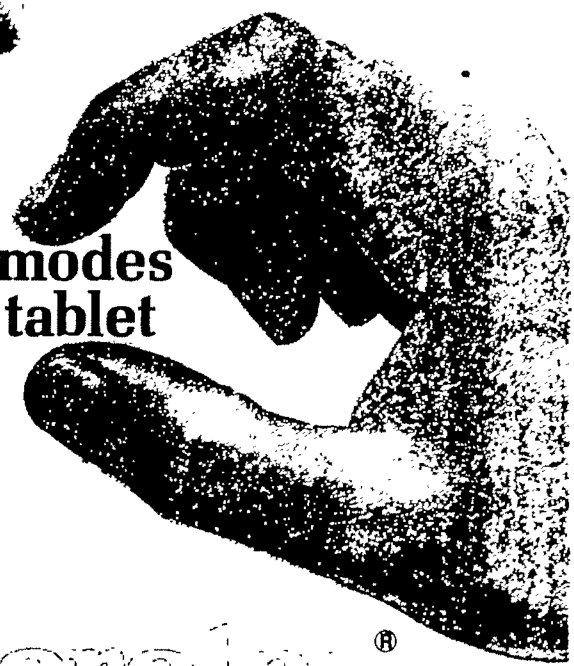

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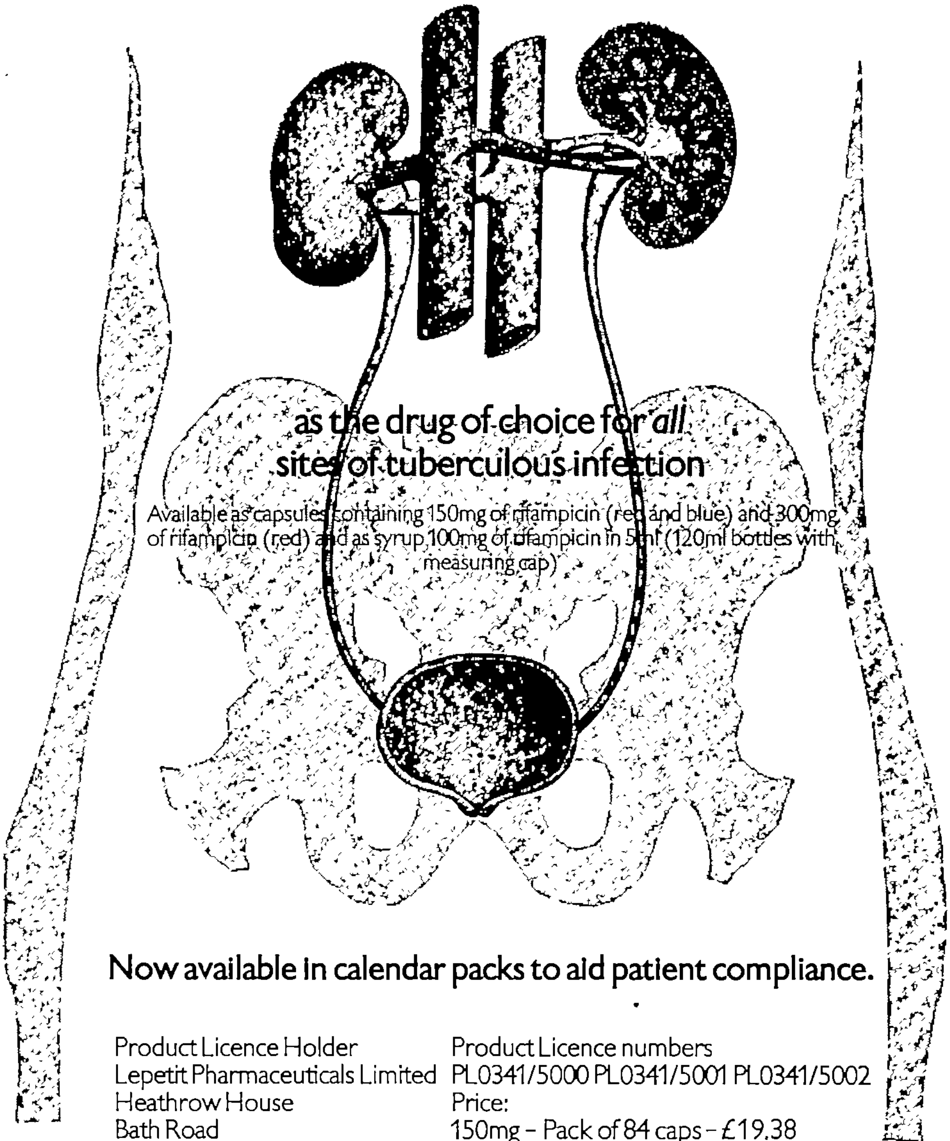

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Lepetit

Clinically he was drowsy and cyanosed with purulent sputum. He weighed 52 kg which was 73% of his predicted weight. The chest radiograph (Fig. 3) was reported as showing widespread emphysema, pulmonary arterial hypertension and a moderately enlarged heart. The heart rate was 110 per minute, blood pressure 90/60 mmHg. There was right ventricular heave, pulsatile liver, ankle oedema, v waves in the jugular venous pulse and engorged retinal veins. Coarse crackles were present at the right base.

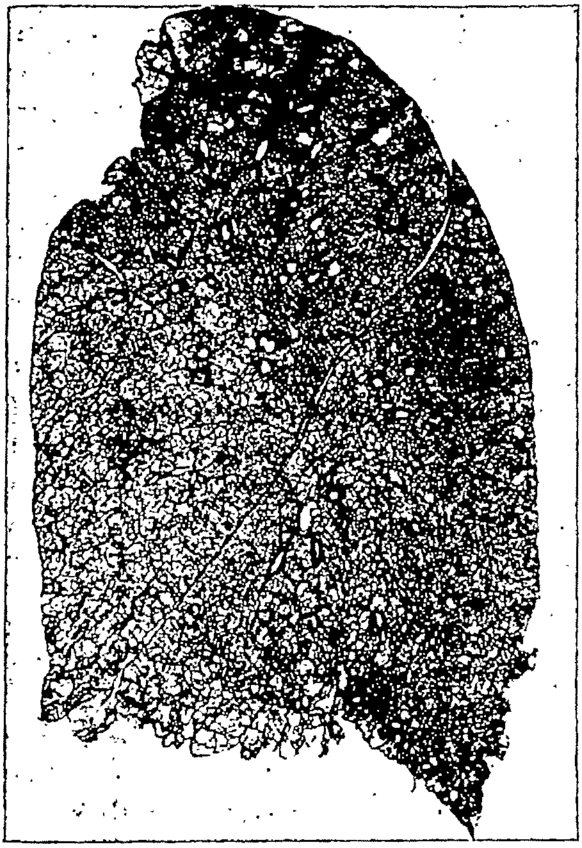

Fig. 2. Case 1. Whole left lung section showing widespread panacinar emphysema

Investigations are itemized as follows: FEV_1 0.4 litres, FVC 1.15 litres, FEV/FVC 34% (predicted 3.35 litre, 4.1 litres and 82% respectively); arterial Po_2 32 mmHg (4.2 kPa), Pco_2 60 mmHg (7.9 kPa); plasma urea 13.0 mmol/litre, sodium 133 mmol/litre, chloride 94 mmol/litre, potassium 5.4 mmol/litre; serum bilirubin 86 μmol/litre, alkaline phosphatase 118 IU/litre, AST 8200 IU/litre, ALT 5700 IU/litre; haemoglobin 16.5 g/dl, white cell count 20.3×10^9/litre (neutrophil leucocytosis), packed cell volume 51 dl/dl. The electrocardiogram showed sinus tachycardia, 110 beats per minute, with features of right ventricular hypertrophy and strain. Because of low weight and relative youth at onset of symptoms a diagnosis of mucoviscidosis was considered but excluded by normal sweat test, glucose tolerance test and faecal fat estimations. Jejunal biopsy was normal.

The illness was managed as chronic bronchitis and emphysema with cor pulmonale and superadded infection leading to right heart failure. Oxygen (Ventimask 24%), frusemide, potassium supplements, intramuscular ampicillin and high doses of corticosteroids were given. There was a good diuresis and his condition had improved after one week.

Further investigations after treatment are itemized as follows: arterial P_{O_2} 39 mmHg (5.1 kPa), P_{CO_2} 41 mmHg (5.4 kPa); bilirubin 230 μmol/litre, alkaline phosphatase 120 IU/litre, AST 55 IU/litre, ALT 208 IU/litre; haemoglobin 18.3 g/dl, white cell count 16.2×10^9/litre, packed cell volume 61 dl/dl; blood volume studies using Cr^{51} labelled red cells and I^{131} labelled human serum albumin: red cell mass 2.3 litres, plasma volume 1.9 litres, blood volume 4.2 litres (predicted 1.6, 2.0, 3.9 litres; Nadler et al. 1962). In view of the increased red cell mass two separate venesections of one unit of blood were performed. His condition gradually deteriorated and he died of respiratory failure five weeks after admission. α_1-Antitrypsin phenotype was reported as PiZZ after death.

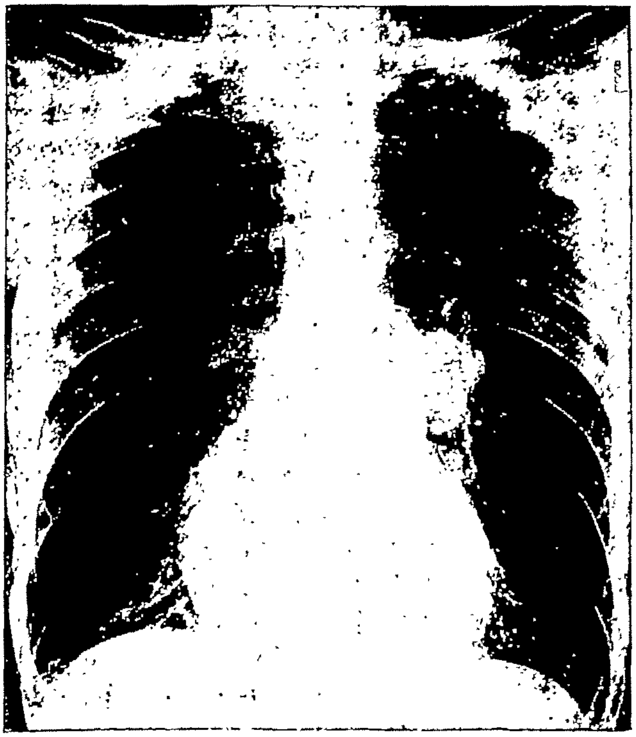

Fig. 3. Case 2. Chest radiograph showing emphysema, large heart and pulmonary arteria hypertension

Autopsy was performed 40 hours after death. Significant findings were confined to the heart, lungs and liver. The heart weighed 500 g (normal range 317 ± 40 g) with right-sided dilatation and right ventricular hypertrophy. Separate weights of right and left ventricle were not taken. Both lungs were heavy, the right weighing 900 g (normal 450 ± 80 g; Whimster & MacFarlane 1974) and the left 880 g (normal 400 ± 90 g). The right lung was inflated and fixed in formalin after which whole lung sections showed widespread panacinar emphysema (Fig. 4). Dissection of left bronchi revealed mucopus and histological examination showed patchy pneumonia. Sections of bronchi showed anthracotic deposits, chronic inflammatory cells and mild increase in mucus secreting glands. The liver weighed only 1070 g (normal range 1200–1500 g) and the cut surface showed marked chronic venous congestion which was confirmed histologically. There was no evidence of cirrhosis. Many of the hepatocytes contained multiple diastase-resistant PAS positive granules.

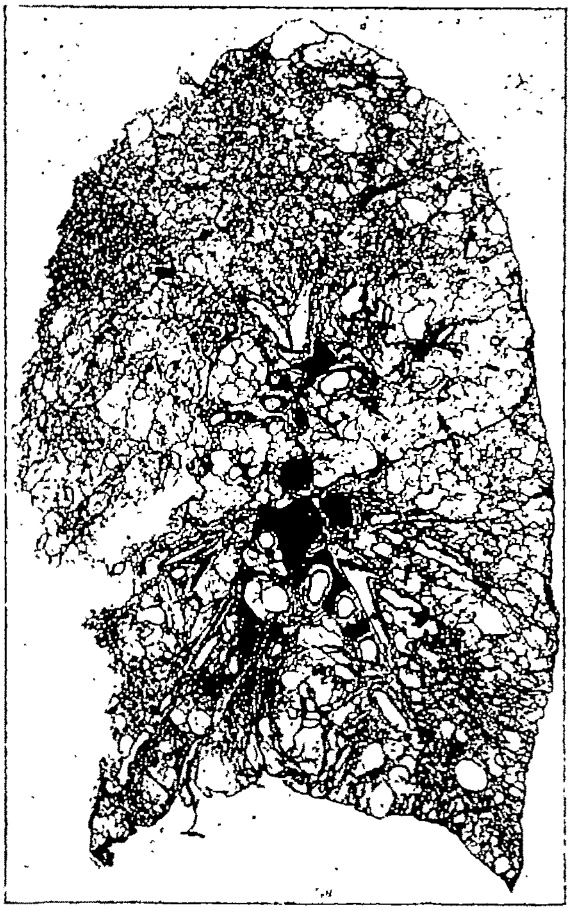

Fig. 4. Case 2. Whole right lung section showing severe widespread panacinar emphysema

DISCUSSION

Incapacitating symptoms usually start in the fourth decade of life in emphysematous patients with alpha-1-antitrypsin deficiency (Hutchison et al. 1971) and these two cases are typical of this premature disability. The cough and spit and histological changes of chronic bronchitis seen here are usual features of the syndrome (Greenberg et al. 1973; Castleman et al. 1973) though the emphysema is generally classified as primary (Eriksson 1965; Welch et al. 1969). Weight loss also is typical (Welch et al. 1969; Hutchison et al. 1971) although it is also a feature of emphysema without α_1-antitrypsin deficiency (Browning & Olsen 1961). Though villous atrophy has been found in association with α_1-antitrypsin deficiency (Greenwald et al. 1975; Sweeney 1975) it was excluded in Case 2 as a cause of weight loss by post-mortem small bowel histology and in Case 1 by antemortem jejunal biopsy.

Markedly abnormal liver function was presumably related to cardiac congestion and improved in Case 2 after control of failure, but liver involvement in α_1-antitrypsin deficiency (Aagenales et al. 1974) characterized by PAS-staining globules (Lieberman et al. 1972) may have been partly responsible. Cirrhosis was, however, absent in both cases despite liver weights being low, conforming with the general experience that it is not usual for the emphysema and cirrhosis of α_1-antitrypsin deficiency to coexist (Lieberman et al. 1972).

A rise in haemoglobin and PCV after diuresis, as in Case 2, is in our experience not uncommon during treatment of cor pulmonale failure, presumably due to unmasking of secondary polycythaemia.

Previous reports emphasize the distribution of emphysema as most advanced in the lower zones both radiographically (Eriksson 1969; Bell 1970) and at post-mortem (Stevens et al. 1971; Greenberg et al. 1973). In Case 1, the radiograph appeared to show predominantly basal emphysema (Fig. 1) but this was not so in Case 2 (Fig. 3). In both our cases, whole lung sections showed emphysema to be severe and widespread (Figs 2, 4). The lungs of Case 2 were heavy and possibly the presence of oedema and widespread pneumonia masked the usual radiological appearance. Bullae were not seen in sections from either patient, nor have they been demonstrated in previous illustrated post-mortem studies (Stevens et al. 1971; Greenberg et al. 1973), despite radiological impressions of basal bullae in this condition. We suspect that 'bullae' reported radiologically in this condition are often avascular areas of severe panacinar emphysema.

In conclusion, the cases demonstrate the typical clinical course of emphysema due to α_1-antitrypsin deficiency. The post-mortem findings were similar to the few previous illustrated published studies, but both our patients appeared to have more widespread distribution of panacinar emphysema than is usual in this condition.

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PULMONARY AND PLEURAL INVOLVEMENT IN ANGIO-IMMUNOBLASTIC LYMPHADENOPATHY

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Summary

A patient with angio-immunoblastic lymphadenopathy is described in whom involvement of the lungs and pleura by characteristic immunoblasts was demonstrated. The literature on pleural and pulmonary involvement in this rare and only recently recognized condition is reviewed.

INTRODUCTION

In recent years a new disease has been described characterized clinically by diffuse lymphadenopathy, hepatosplenomegaly and polyclonal hypergammaglobulinaemia and occasionally complicated by haemolytic anaemia. Specific histological changes have been noted in lymph nodes and other affected tissues. The name angio-immunoblastic lymphadenopathy has been applied to this lymphoma-like disorder. In a few cases pulmonary and pleural involvement have been documented. We report the case of a patient in whom such intrathoracic manifestations were prominent: such a case has not been previously described in the British literature.

Case Report

A 59-year-old despatch clerk was referred to the Brompton Hospital in May 1977. He had smoked 20 cigarettes daily for 40 years. He complained of progressive breathlessness on effort for 12 months and a dry cough for two months, together with recent malaise and occasional fever. On examination early finger-clubbing was noted. The breath sounds were diminished in all lung zones and fine inspiratory crackles were audible at both lung bases. The cardiovascular system, abdomen and nervous systems were normal to examination. A chest radiograph showed bilateral hyperinflation and diminished vascular markings in the right upper zone. Septal lines and streaky shadowing were noted at both bases. The heart was not enlarged. An electrocardiogram was unremarkable. Respiratory function tests showed a severe obstructive ventilatory defect with hyperinflation and air-trapping. Airway resistance was increased and carbon monoxide transfer factor reduced. The haemoglobin was 14.9 g/dl and the total white cell count 11 600/mm^3 of which 500 were eosinophils. Antinuclear factor, rheumatoid factor and avian precipitins were all absent. When seen two months later he complained in addition of anorexia and abdominal distension. Finger-clubbing was unequivocal. Pathological lymphadenopathy was noted in both cervical and supraclavicular groups and both axillae and inguinal regions. Hepatomegaly to 8 cm and splenomegaly to 2 cm were present. A chest radiograph demonstrated an increase in the prominence of the septal lines and of the basal shadowing. Small bilateral pleural effusions were present. Histology of an excised cervical lymph node and of a small nodule on the anterior chest wall revealed changes characteristic of angio-immunoblastic lymphadenopathy. The degree of hepatosplenomegaly rapidly increased and the patient's condition deteriorated. The haemoglobin was 11.5 g/dl, the total white cell count 19 000/mm^3 of which 87% were neutrophils, and the ESR

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WIDESPREAD PANACINAR EMPHYSEMA WITH ALPHA-1-ANTITRYPSIN DEFICIENCY

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Summary

We report the clinical, laboratory and necropsy findings in the cases of two patients with homozygous α_1-antitrypsin deficiency with a widespread distribution of panacinar emphysema.

INTRODUCTION

Homozygous α_1-antitrypsin deficiency occurs in approximately 1 in 1750 of a Swedish population (Eriksson 1965) and in 1 in 3450 of a UK population (Cook 1975) but between 1% (Kueppers et al. 1964) and 13% of subjects with radiological pulmonary emphysema (Hutchison et al. 1971) and in as many as 48% of subjects with emphysema under 50 years of age (Lieberman 1969). There are reports in the world literature of post-mortem data (Stevens et al. 1971; Castleman et al. 1973; Greenberg et al. 1973) but few in the British literature (Sweeney 1975) and all stress a basal distribution of the emphysema in such patients.

Case Reports

Case 1

A 37-year-old housewife was admitted urgently with breathlessness, lassitude and ankle swelling. She had smoked 20 cigarettes daily for 20 years till several months before admission when she stopped because of symptoms. There had been productive cough for seven years and progressive breathlessness over the previous two years. A diagnosis of α_1-antitrypsin deficiency (phenotype PiZZ; Cook 1975) had been made before admission.

On examination she was drowsy, cyanosed and produced clear sputum. She weighed 41.3 kg which was 78% of her predicted weight for sex, height and age (Society of Actuaries, Chicago, 1959). A chest radiograph showed predominantly basal emphysema (Fig. 1). The heart rate was 120 per minute, blood pressure 110/70 mmHg. The liver was palpable three finger-breadths below the costal margin, the jugular venous pulse was elevated to the angle of the jaw and there was slight sacral and ankle oedema.

The investigations are itemized as follows: FEV_1, 0.38 litres, FVC 0.94 litres and FEV_1/FVC 40% (predicted 2.3 litres, 2.6 litres and 88% respectively) (Cotes 1975); arterial $P\mathrm{o}_2$ 29 mmHg (3.8 kPa), $P\mathrm{co}_2$ 79 mmHg (10.5 kPa); plasma urea 11.0 mmol/litre, sodium 135 mmol/litre, chloride 81 mmol/litre, potassium 5.1 mmol/litre; serum bilirubin 42 μmol/litre (normal range 5–17 μmol/litre), alkaline phosphatase 242 IU/litre (normal 21–106 IU/litre), asparate aminotransferase (AST) 954 IU/litre (normal 13–42 IU/litre), alanine aminotransferase (ALT) 1237 IU/litre (normal 10–55 IU/litre); haemoglobin 14.1 g/dl, white cell count 12.7 × 10^9/litre, packed cell volume 47.7 dl/dl. The electrocardiogram showed sinus tachycardia, 110 beats per minute, with p pulmonale and features of right ventricular hypertrophy.

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The illness was managed as an exacerbation of bronchitis with respiratory failure and right heart failure. She was given oral co-trimoxazole, oxygen (Ventimask 24%), frusemide and potassium supplements. After two days without clinical improvement doxapram infusion was started. She deteriorated and died four days after admission.

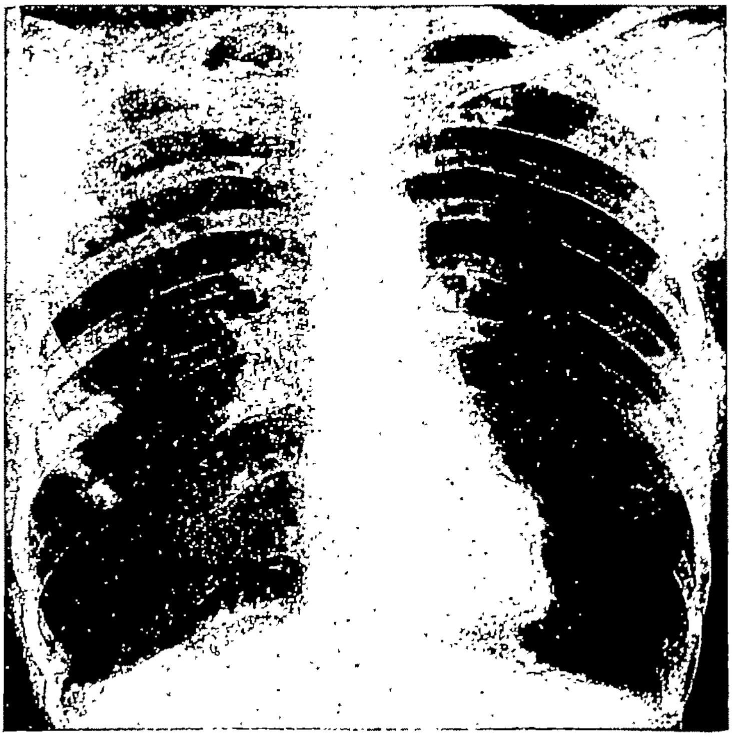

Fig. 1. Case 1. Chest radiograph showing predominantly basal emphysema

Autopsy was performed 18 hours after death. The heart weighed 280 g (normal range for height and sex 259 ± 30 g; Zeek 1942) with marked right ventricular hypertrophy, the right ventricle weighing 87 g (normal < 80 g; Fulton et al. 1952). The pulmonary artery showed flecks of atheroma. The voluminous lungs showed air trapping. They were preserved together for fixing in formalin and were not weighed individually. Whole lung sections were subsequently prepared by the technique of Gough and Wentworth (1960) and showed severe widespread panacinar emphysema (Fig. 2). Histology of major bronchi showed only mild hypertrophy of mucus glands. The liver weighed 900 g (normal range 1200–1500 g; Sherlock 1971), the cut surface showing chronic venous congestion but no cirrhosis. Histology showed multiple PAS-staining disease-resistant globules within periportal hepatocytes consistent with α_1-antitrypsin deficiency (Lieberman et al. 1972). Small bowel histology showed normal villous pattern.

Case 2

A 42-year-old man was admitted to hospital as an emergency with breathlessness, ankle swelling and drowsiness. He had smoked 20 cigarettes daily for eight years but had stopped in his early twenties with productive cough. He worked as a labourer in the building trade until breathlessness at rest had forced him to give up work nine years before hospital admission.

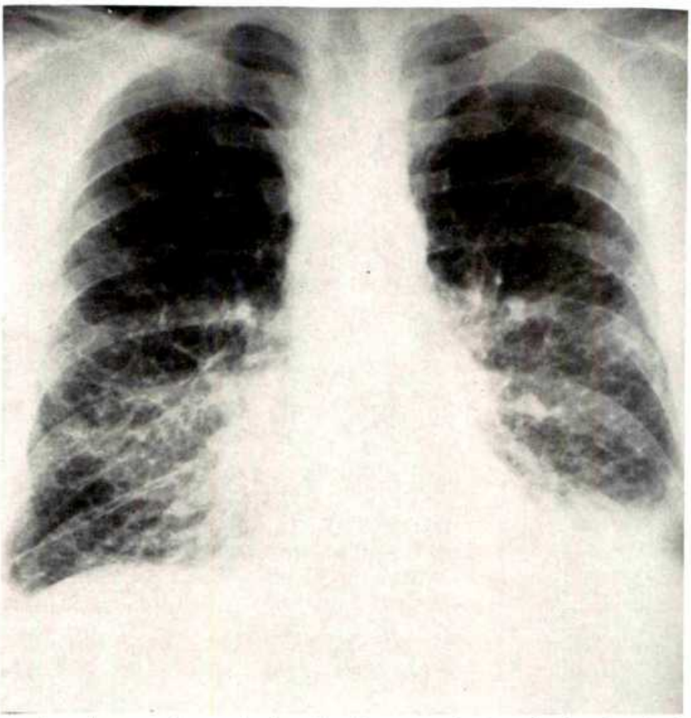

Fig. 1. Posteroanterior chest radiograph showing heavy reticular shadowing in both lower zones and a left basal effusion

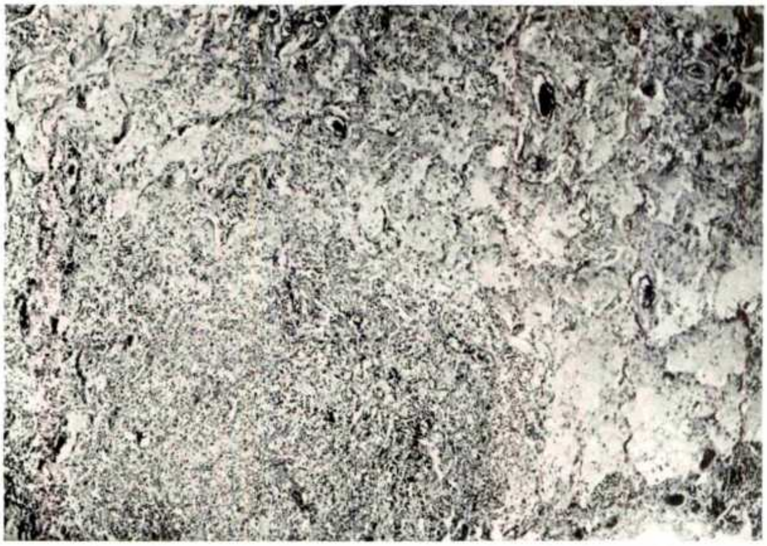

Fig. 2. Low-power photomicrograph of autopsy specimen from left lower lobe. On the left of the picture there are some normal alveoli. On the right the alveoli can be seen to be filled with darkly staining cells. × 42

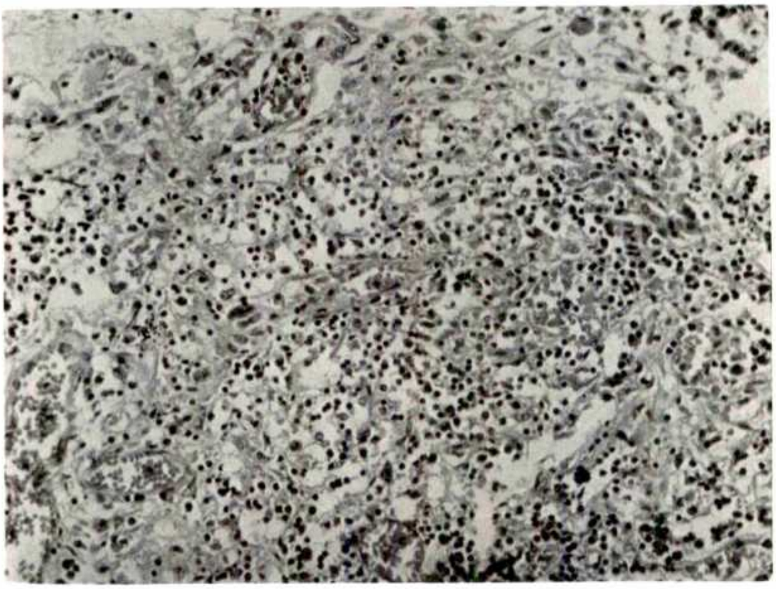

Fig. 3. Higher magnification showing numerous blood vessels and darkly staining round cells filling many of the alveolar spaces. ×160

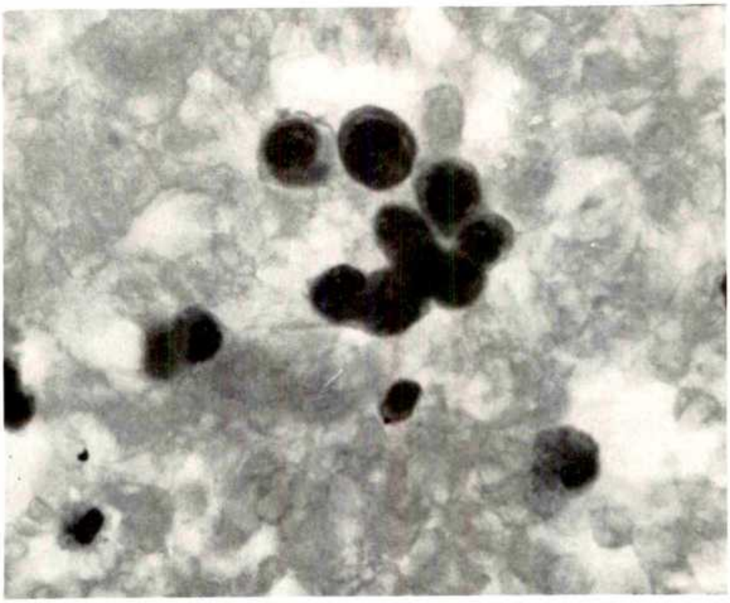

Fig. 4. Photomicrograph of pleural fluid. In the centre of the field there is a clump of large round cells with darkly staining nuclei characteristic of immunoblasts.

28 mm in the first hour. The alkaline phosphatase was raised to 21 King-Armstrong units. The IgG was grossly elevated, and IgA and IgM were at the upper limit of normal. Aspiration of the left pleural effusion yielded blood-stained fluid containing immunoblasts similar to those seen in the lymph node biopsy. High-dose oral corticosteroid administration was started. However, the patient died of overwhelming chest infection, which did not respond to antibiotics, four months after the first abnormal chest radiograph.

Autopsy

Bilateral blood-stained pleural effusions were present. Nodules of tumour about 2 mm in diameter were noted on the visceral pleura overlying the left lower lobe. Histology of these revealed characteristic changes of angio-immunoblastic lymphadenopathy. Severe centrilobular emphysema and bullae were noted in both upper lobes and similar changes of less severe degree in both lower lobes. Dilatation of peripheral bronchi characteristic of chronic airway obstruction was present. The lymphatics and blood vessels were grossly normal. Histology of the left lower lobe showed severe interstitial fibrosis of the alveolar walls with clusters of immunoblasts in the subpleural alveolar walls. The lymph nodes in the cervical, supraclavicular, para-aortic and mesenteric groups were all enlarged and histologically showed changes characteristic of angio-immunoblastic lymphadenopathy.

Discussion

The report describes a patient with chronic airway obstruction presenting in addition with an acute illness whose nature was not appreciated until the development of lymph node enlargement and hepatosplenomegaly. Pulmonary and pleural involvement were prominent throughout this short illness.

Angio-immunoblastic lymphadenopathy was first described by Frizzera et al. in 1974 in a series of 15 patients, mainly elderly, presenting with an acute onset of systemic upset, with diffuse lymphadenopathy, hepatosplenomegaly and immunological abnormalities including autoimmune haemolytic anaemia and hypergammaglobulinaemia. The clinical picture is easily confused with malignant lymphoma, but the histological features are quite specific. There is pronounced proliferation of small vessels with a hyperplastic endothelium, a cellular infiltrate rich in immunoblasts and often an eosinophilic material between the cells. The disease is thought not to be neoplastic but probably represents a reaction to an as yet unidentified stimulus. The immunoblast is thought to be of B-cell origin (Valdes & Blair 1976).

In 1975, Lukes and Tindle reported a series of 32 cases accumulated over a period of 12 years and further characterized the natural history of the disease. In 18 fatal cases, the median survival was 15 months. In three cases evolution to a frankly malignant condition, named immunoblastic sarcoma, was noted. Frizzera et al. (1975) presented a comprehensive report on 24 cases including the 15 described in their first report of 1974. In their paper (1975) intrathoracic lesions were described for the first time. Nine patients had mediastinal and hilar lymphadenopathy and in two pulmonary infiltrations were noted. One patient had a diffuse nodular infiltrate, predominantly basal in distribution and three had small bilateral pleural effusions. In one patient, multiple lung biopsies revealed the alveolar walls to be lined by hypertrophic granular pneumocytes and the alveoli to be filled with immunoblasts. No vasculitis, granulomas or necrosis were noted.

Since these publications, three further reports of pulmonary and pleural involvement in angio-immunoblastic lymphadenopathy have appeared and a fairly uniform clinical picture has emerged (Iseman et al. 1976; Zylak et al. 1976. The pulmonary shadowing is generally restricted to the mid- and lower zones and is usually coarse and nodular or reticulonodular. The lesions may regress spontaneously (Iseman et al. 1976) or may respond to corticosteroids (Zylak et al. 1976) or cyclophosphamide and vincristine. Histologically the appearances may be of non-specific interstitial infiltration, or specific infiltration with immunoblasts may be seen. In one case (Iseman et al. 1976) immunofluorescence revealed focal intracellular deposition of IgG and IgM in the alveolar walls. Pleural effusions have usually been small and bilateral: the finding of immunoblasts in the pleural fluid both in life and at autopsy as in the present case has not been previously recorded.

ACKNOWLEDGEMENTS

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CEREBRAL ASPERGILLOMA IN A PATIENT WITH ALLERGIC BRONCHOPULMONARY ASPERGILLOSIS

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Summary

The case is described of a woman of 21 who had suffered since childhood from asthma and allergic bronchopulmonary aspergillosis. During her recovery from a period of severe status asthmaticus she developed widespread patchy lung shadowing, signs of an intracerebral space-occupying lesion and high titres of serum precipitins to *Aspergillus fumigatus*. Post-mortem examination revealed *Aspergillus* bronchopneumonia and an intracerebral aspergilloma.

INTRODUCTION

Disease caused by *Aspergillus fumigatus* can take four forms as described by Virchow (1856). These are (*a*) bronchial, with or without sensitization (Henderson et al. 1968; McCarthy & Pepys 1971); (*b*) mycetoma (McCarthy & Pepys 1973); (*c*) pneumonic, invasive or necrotizing (Kennedy et al. 1970); and (*d*) disseminated (Gowing & Hamlin 1960; McCormick et al. 1975). The bronchial type with sensitization corresponds to the type defined by Hinson et al. (1952) and now referred to as allergic bronchopulmonary aspergillosis. This condition has the following diagnostic features: attacks of reversible airway obstruction, recurrent transient opacities on the chest radiograph, sputum and blood eosinophilia and allergy to *Aspergillus fumigatus* as demonstrated by an immediate (Type I) and a delayed (Arthus, Type III) skin reaction to *Aspergillus* protein (Safirstein et al. 1973).

We report here a case of disseminated aspergillosis occurring in a patient with long-standing allergic bronchopulmonary aspergillosis.

Case Report

The patient was born in October 1954 and developed bronchial asthma at the age of eight years. At the age of 18 years she suffered a typical episode of allergic bronchopulmonary aspergillosis with eosinophilia, a positive Type I skin reaction and positive serum precipitins to *Aspergillus fumigatus*, and an opacity in the left upper zone on chest radiograph that responded rapidly to treatment with prednisone. In December 1973 she suffered an identical episode and in October 1974 and in July 1975 there were two similar episodes, although these were unaccompanied by transient pulmonary opacities. Treatment of each exacerbation included prednisone 40 mg daily and on each occasion this was tailed off over three to four months. She was maintained on disodium cromoglycate, beclomethasone dipropionate by inhalation and oral bronchodilators. From October 1974 she was never completely free of wheeze.

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On 8 February 1976 she developed an infection with influenza A followed by a productive cough and severe wheezing. The chest radiograph showed no abnormal shadowing and *Aspergillus* precipitins were absent from the serum as they had been in both October 1974 and July 1975.

Despite intensive treatment with corticosteroids and bronchodilators, her condition continued to deteriorate and by 11 February she required mechanical ventilation. She received intravenous salbutamol, gentamicin and erythromycin and there was a slow improvement over five days, after which the tube was removed. The white cell count was 35×10^9/litre with 98% neutrophils and newly-developed crepitations were audible over the whole chest. There was patchy radiological shadowing in both mid-zones (Fig. 1) and both *Pseudomonas aeruginosa* and *Aspergillus fumigatus* were cultured from her sputum.

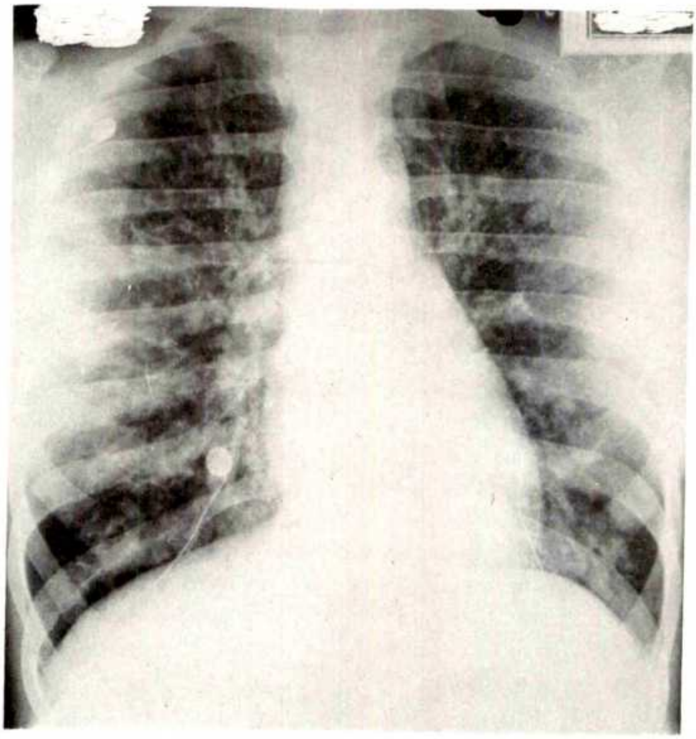

Fig. 1. Chest radiograph showing new patchy shadowing in both mid-zones

She remained drowsy and confused until 23 February when it was noticed that her right pupil reaction was sluggish, she had a grasp reflex in her right hand, absent knee and ankle jerks and bilateral extensor plantar responses. She was continuing to receive high doses of corticosteroids, gentamicin and colistin. Her white cell count was 46×10^9/litre, her ESR was 144 mm/hour and the serum was strongly positive for precipitins to *Aspergillus fumigatus*. Lumbar puncture revealed a CSF pressure of 220 mm, a protein of 1.8 g/litre, a glucose of 2.9 mmol/litre, 4.67×10^9/litre red cells and 1.58×10^9/litre white cells. Cultures were sterile but the fluid was weakly positive for precipitins to *Aspergillus fumigatus*.

An EMI scan of the brain confirmed a space-occupying lesion deep in the left frontoparietal region with considerable surrounding oedema. A left frontal burr hole was made, but her level of consciousness deteriorated steadily and she died on 25 February.

Post-mortem examination showed both lungs to be extensively involved with bronchopneumonia and to contain numerous cavities with congested walls. The left frontal lobe of the brain was soft

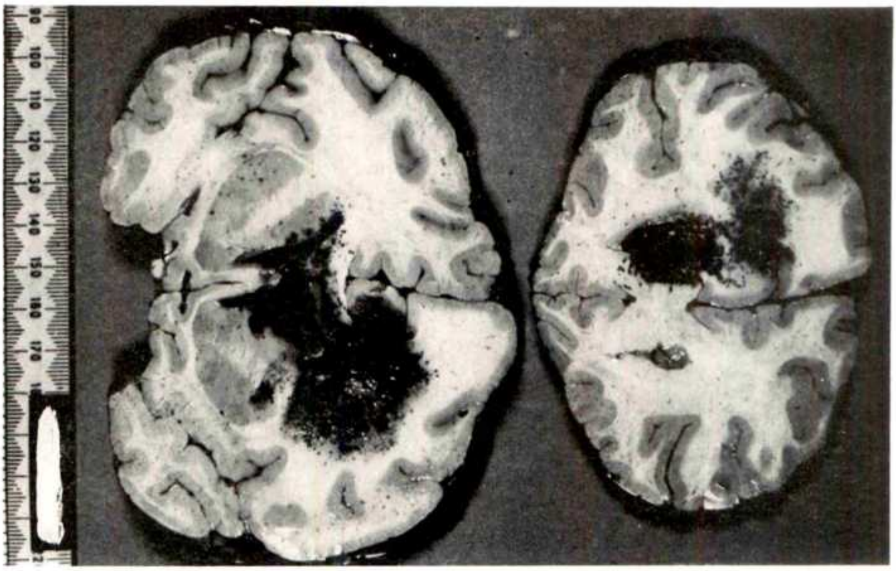

Fig. 2. Post-mortem appearance of the brain cut vertically to expose a haemorrhagic cavitating lesion in the left frontal lobe

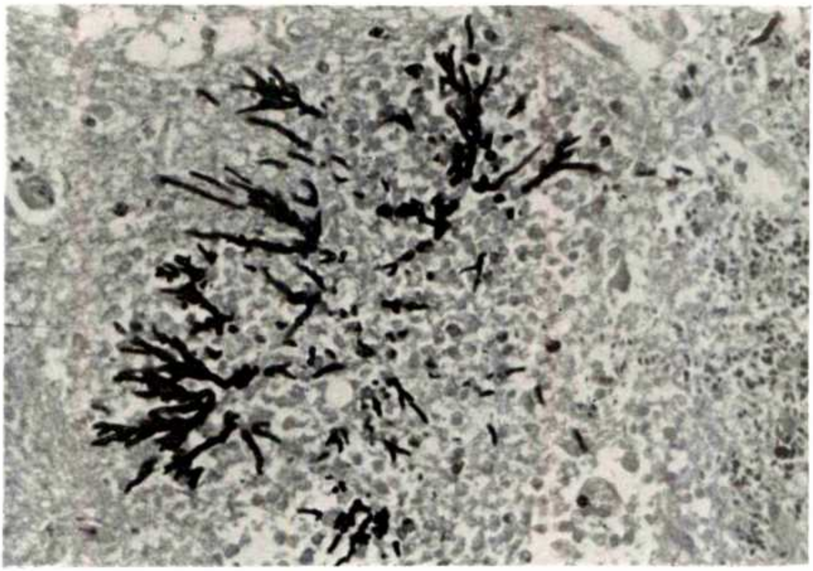

Fig. 3. Fungal hyphae typical of *Aspergillus fumigatus* in a section from the involved brain. Grocott stain, × 175

and contained a central cavity partially filled with orange granular material (Fig. 2), and there was herniation of the left temporal lobe. Histology showed the wall of the intracerebral cavity to be invaded by branching septate hyphae typical of *Aspergillus fumigatus* (Fig. 3). The pulmonary tissue showed pneumonia and abscess formation with similar fungal hyphae.

DISCUSSION

Limited invasion of lung tissue has been described in patients with allergic bronchopulmonary aspergillosis (Riley et al. 1975; Henderson et al. 1968) and in a patient after infection with influenza A (Abbott et al. 1952). The development of a pulmonary mycetoma has been reported in a young asthmatic with allergic bronchopulmonary aspergillosis who had received treatment with penicillin and prednisone (Safirstein 1973). To our knowledge, however, there has been no previous report of a case of disseminated aspergillosis occurring in a patient with documented allergic bronchopulmonary aspergillosis.

Conversely, in disseminated aspergillosis, with involvement of non-pulmonary tissues, none of the reported cases has been shown to have allergic bronchopulmonary aspergillosis (Vedder & Schorr 1962; Burke et al. 1970; Young et al. 1970; Grossman 1975) although Shapiro and Tabaddor (1975) among four patients with cerebral aspergillomata described one with 10% eosinophilia and raised serum IgE who developed *Aspergillus* pneumonitis.

Under appropriate predisposing circumstances, the possibility of disseminated *Aspergillus* infection should be borne in mind when an ill patient with aspergilli in the sputum develops new radiological lung shadowing and has serum precipitins to *Aspergillus fumigatus*. The present case demonstrates that this is so even when the patient in question is known to have allergic bronchopulmonary aspergillosis.

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TREATMENT OF A RUPTURED HYDATID CYST OF LUNG WITH MEBENDAZOLE

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Summary

Mebendazole was given prophylactically to a patient with a ruptured pulmonary hydatid cyst before surgical excision of the cyst. The cyst size was reduced by half and there was no radiological or immunological evidence of the presence of active secondary disease 15 months after rupture. The primary cyst was invaded by fungal hyphae, probably *Aspergillus*, and the danger of abscess or mycetoma formation if surgery is not carried out after chemotherapy is emphasized.

INTRODUCTION

Cystic hydatid disease due to *Echinococcus granulosus* infection normally requires surgical excision, though undiagnosed cysts have occasionally been known to calcify after several years if the parasite dies naturally.

Surgical excision of a hydatid cyst is curative if the cyst is removed intact before rupture. There is a grave danger that live daughter cysts will be disseminated in the lungs if the cyst ruptures and in time will also require additional surgery. This paper reports the treatment of a ruptured hydatid pulmonary cyst with mebendazole and the subsequent sequelae.

Case Report

A male farmer aged 56 was first seen in June 1978 with a history of a productive cough and left pleuritic pain during the previous three weeks. His son had had a hydatid cyst of the liver nine years previously. His general condition was good and physical examination revealed only a few râles at the base of the left lung. Chest radiographs showed a large oval opacity 6 × 4 cm containing air in the left lower lobe. Liver ultrasound scan was normal as were blood count, serum urea and electrolytes, liver function tests and culture and cytology of urine. Hydatid complement fixation test was positive (1/8) but this was not considered significant in an endemic area. Immunophoresis of blood proteins was normal. Sputum cultures were negative for organisms including tubercle bacilli. Cytology of sputa showed squamous metaplastic changes on three occasions, but no carcinoma cells were seen.

A tentative diagnosis of a ruptured pulmonary hydatid cyst was made.

As a prophylactic measure against secondary seeding by daughter cysts from the already ruptured primary cyst during an operation we contemplated giving a high dosage of the anthelmintic mebendazole of 400 mg three times a day as described by Behkti et al (1977). for the treatment of inoperable hydatid cysts of the liver. However, the dosage had to be reduced to 100 mg three times a day for two weeks because the patient vomited after the first two doses. No side effects were noted apart from blood-stained sputum on the third and fourth days and indigestion on the eighth and ninth days. The dosage was increased to 300 mg three times a day for another week without further symptoms and he completed a three-week course totalling 10.5 g of mebendazole.

The patient felt much better, recovered a good appetite, put on 9 kg in weight and had no chest pains, cough or sputum. Blood count including platelets remained normal, as did liver function tests. Total IgE was raised at 535 IU/ml (normal 500 IU/ml). The chest radiograph one month after commencing chemotherapy showed a slight reduction in size of the left lower lobe opacity. A second course of mebendazole was commenced three weeks later at a higher dose of 300 mg three times a day but this was discontinued after five days because of exertional dyspnoea and cough. The mebendazole was resumed a week later on amelioration of these symptoms and in the absence of any worsening of the chest radiographic appearances. It was then increased to 400 mg three times a day for four weeks without further incident. More courses of the drug were not given because of the onset of epigastric pain. The patient thus had a total of 48.6 g during the two courses of treatment. His chest radiograph after his second course of treatment showed a reduction in the size of the left lower lobe opacity to 3 cm diameter, i.e. over 50% regression. Liver function tests, blood count and urea remained normal. Operation was carried out two months later and a hydatid cyst which was totally collapsed to about the size of a walnut was removed. There was a good deal of necrotic material in the cavity and the bronchial fistula was rather larger than usual. Histology confirmed an opened cyst 6 cm diameter with hydatid hyaline membrane and inflammatory changes with branching septate fungal hyphae, probably *Aspergillus*.

Convalescence was uneventful as far as his chest was concerned and his total IgE dropped to 60 IU/ml. A micro-ELISA test three weeks after operation showed antibody titre <1:50 in the IgM fraction. The antibody in the IgG was 1:200. Five months after operation IgE was 11 IU/ml and an ELISA test showed no evidence of IgM antibody and a low titre of IgG antibody. The serum precipitins for *Aspergillus fumigatus* and *A. niger* were negative at the same time. A chest radiograph 10 months after operation showed no evidence of pulmonary disease.

DISCUSSION

Any alternative to surgery would be a welcome advance in the treatment of *Echinococcus granulosus* infection. An aggressive surgical approach is usually recommended with removal of the cysts from the lungs, liver and other organs followed by long-term surveillance for secondary cyst recurrence. Wilson et al. (1968), in their review of reports from other areas, quoted mortality rates on long term follow-up of between 0 and 30% in the pastoral-type disease described above, and secondary or recurrent echinococcal infection rates of 2–14% in patients with lung cysts and 0–11% in patients with hepatic cysts. Behkti et al. (1977) treated four patients with hepatic cysts with high-dosage mebendazole which reduced the cysts to scars after two or three courses without side-effects. Our patient had obviously suffered a rupture of his pulmonary cyst with leakage causing pleuritic symptoms of three weeks duration and it was considered that mebendazole therapy in high dosage might be effective in destroying any live daughter seedlings, if not the parent embryo, which would have to be removed surgically. The development of gastric side-effects necessitated a lower dosage level but early results with this dosage were impressive, with improved general health and definite reduction in the size of the cyst during the first month. A further course at high dosage for a month reduced the cyst further to about half the original size. The surgical specimen confirmed the reduced size of the cyst and the presence of an inflammed hyaline membrane.

The invasion by fungal hyphae resembling *Aspergillus* in a ruptured evacuated and presumably sterilized cyst resembles that in healed tuberculous cavities and introduces a potential hazard of abscess or mycetoma formation. Because of this possible complication, we suggest that surgical excision should complete the treatment where rupture or

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G. Cumming B.Sc. Ph.D. D.Sc. M.B. Ch.B. F.R.C.P. and S.J. Semple M.D. M.B.B.S. F.R.C.P. Second Edition, May 1980. 680 pages, 80 illustrations. Cloth about £30.00, paper about £17.50

The success of the first edition of this book ensured a rapid sale on both sides of the Atlantic with a result that it has unfortunately been unavailable for some time. This has however given the authors an opportunity to revise their text to bring it up to date and to incorporate recent developments which lead to a greater understanding of lung physiology. It has been designed to provide both undergraduates with a text which will enable them to relate their basic training to their forthcoming clinical studies, and as a comprehensive reference for postgraduates with an interest in chest disease.

Respiratory Diseases

J.Crofton M.A. M.D. F.R.C.P. and A. Douglas M.B. Ch.B. F.R.C.P. Third Edition, in preparation

Diagnosis and Management of Respiratory Diseases

G.K. Crompton M.B. F.R.C.P.E. June 1980. 272 pages, 5 illustrations. Paper, about £8.50

This book is designed to develop an understanding of the practical aspects of diagnosis and management in undergraduate students and junior staff in training. The essentials of respiratory disease are crystallised from a background of basic science and the most important aspects are summarised at the end of each chapter. The benefit of the author's considerable experience is passed on to his readers in this stimulating text.

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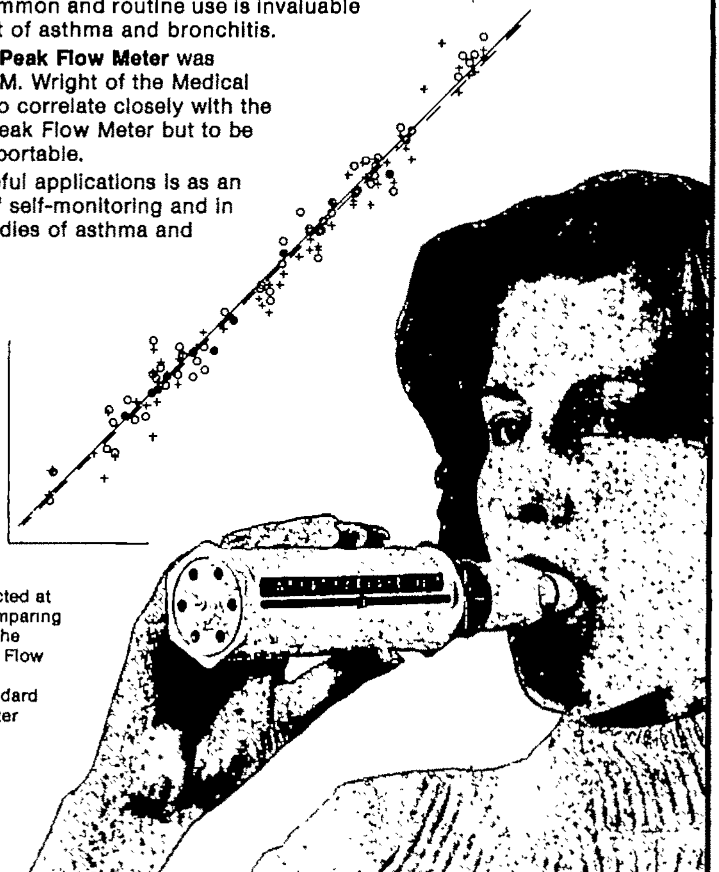

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Br. J. Dis. Chest (1980) *74,* 309

THE BRITISH THORACIC ASSOCIATION

A meeting of the Association, jointly with the Welsh Thoracic Society, was held at the University of Swansea on 9–11 April 1980.

The President announced that Mr L. D. Booker, who had been Administrative Secretary of the British Thoracic and Tuberculosis Association for many years, had died on 12 November 1979. Members of the Association stood in respect for his memory.

The following papers were then read.

The Current Status of BCG Vaccination

I. Sutherland
MRC Unit, London

The disappointing results in the large-scale controlled trial of two strains of BCG vaccine against tuberculosis in South India have not so far been explained, though some possible explanations were aired. The findings are, however, not relevant to the situation in Britain, where the BTA survey (reported to the 1979 annual conference and now published in the *British Journal of Diseases of the Chest*) showed more than 70% protection against tuberculosis for at least ten years after vaccination. The implications of this and other findings for the best use of BCG vaccination in Britain were considered.

Technical Aspects of BCG Vaccine

P. W. Muggleton
Glaxo Group Research Ltd.,
Greenford, Middx.

The introduction of freeze-dried BCG vaccine was a major step forward because this allowed the product to be standardized before use. In particular, pairs of vaccines, matched in terms of content of living (and dead) organisms, could be compared clinically. From these studies it has become evident that differences exist between the various substrains of BCG and also that the method of manufacture of the vaccine may have different effects on the protective and tuberculin allergizing potencies and that these may be unrelated. These differences may be correlated with the colonial morphology of the BCG.

Administration of BCG vaccine by the intradermal route may be done by syringe and needle or by various jet injectors. The relative merits of these, and their demands on the potency of the vaccine, are of clinical relevance. The need for a simple, fool-proof method of giving BCG on a mass scale, and the difficulties in developing a multipoint applicator for this purpose, were outlined.

The Relationship between Positive Skin Tests and Tuberculin Coating in Tine Testing

J. A. Lunn
St Mary's Hospital, Paddington

Hong Kong Chest Service/Tuberculosis Research Centre Madras/British Medical Research Council Study of Three-month and Two-month Regimens for Smear-negative Pulmonary Tuberculosis: Results up to 30 Months

D. J. Girling
MRC Chest Diseases and Tuberculosis
Unit, London

It is uncertain what proportion of patients with radiographically and clinically 'active' pulmonary tuberculosis, but whose sputum smears are repeatedly negative for acid-fast bacilli, require antituberculosis chemotherapy, or, for those who do need treatment, what duration is adequate. The duration of chemotherapy appropriate for patients with consistently smear-negative but culture-positive findings is also as yet unsettled.

In this study, 1212 Chinese patients, diagnosed at meetings of chest physicians from the Hong Kong Chest Service as having radiographically active pulmonary tuberculosis, but with sputum negative for acid-fast bacilli on five recent smear examinations, and who had not previously received anti-tuberculosis chemotherapy, were randomly allocated to one of the four series:

1. SC. Selective chemotherapy. Antituberculosis chemotherapy was not started until the activity of the tuberculosis had been confirmed bacteriologically on the initial or subsequent cultures, or by radiographic or clinical deterioration.
2. 2SHRZ. Streptomycin, isoniazid, rifampicin and pyrazinamide in standard dosages daily for two months.
3. 3SHRZ. The same as 2 above, for three months.
4. SPH/S_2H_2. A standard control regimen of streptomycin, PAS and isoniazid daily for three months, followed by streptomycin and high-dosage isoniazid twice a week for nine months.

The results up to 30 months were presented.

Two Years' Experience of Antituberculous Chemoprophylaxis in Asian Immigrants

M. W. McNicol and C. J. Allen
Willesden Chest Clinic, London

The Effects of Spinal Fusion on Lung Function in Idiopathic Scoliosis

D. Siegler and P. A. Zorab
Cardiothoracic Institute, London

In many previously published studies, whatever the cosmetic or other advantages of spinal fusion in patients with idiopathic scoliosis, short-term follow-up has failed to reveal any significant improvement in lung function as a result of such surgery. In order to ascertain whether spinal fusion benefits lung function in the long term, 39 volunteer adult patients in whom spinal fusion had been performed were studied. The interval between surgery and the lung function estimations ranged from 9 to 28 years. Simple spirometry, subdivisions of lung volume and carbon monoxide transfer factor were estimated and compared with results obtained in a group of 35 volunteer adults with idiopathic scoliosis of comparable severity at the time of the study who had not undergone surgery. Patients with unrelated cardiac or pulmonary diseases were excluded. All physiological variables were expressed as percentages of the mean predicted values for age, sex and height. Such a study of adult scoliotics eliminates any differences between the groups due to the adolescent 'growth spurt'.

In most respects, the lung function results were significantly closer to predicted values in the non-operated group. However, because we do not have adequate preoperative data in the operated group, we cannot eliminate the possibility that spinal fusion enabled the operated group, whose degree of angulation was greater prior to surgery, to 'catch up' to some extent with patients with scoliosis of lesser severity.

Radiological Changes in Coalminers on Leaving the Industry

A. Seaton, C. A. Soutar and A. W. T. Melville
Institute of Occupational Medicine, Edinburgh

2094 ex-miners were studied in a nationwide epidemiological survey and compared with 1755 men who were still working in the industry. All these men had previously taken part in the National Coal Board's Pneumoconiosis Field Research. Comparisons were made between radiographs taken towards the end of their period of employment and those taken at the time of the follow-up survey. Simple pneumoconiosis was found to show both apparent progression and regression after leaving the coal industry and such changes, agreed independently by three readers, occurred in approximately 1% of cases in both directions. Massive fibrosis was also shown to occur for the first time after leaving the industry in small numbers of men.

The Pathological Counterparts of Radiographic Types of Small Rounded Opacity

V. A. Ruckley and A. Seaton
Institute of Occupational Medicine, Edinburgh

During the first phase of the Autopsy Study undertaken at the Institute 500 sets of lungs were examined. A radiograph taken within four years of death was available for 261 of these cases. The radiographs were read by a panel of four doctors from the National Coal Board X-ray service. It was noted that in a proportion of cases at least three readers agreed on the type of small rounded opacity present. This seemed an appropriate group in which to examine whether a particular type of opacity represented a uniform pathological pattern. From the group one observer selected a number of radiographs showing typical appearances of each type of small rounded opacity and added a proportion of cases categorized as O/O to give a total of 31 cases for study.

A single lung slice from each case was examined by four observers who had no knowledge of the radiographic classification. Foci of dust deposition were counted within three size ranges and the predominant lesion shape was recorded. Without prior discussion of specific criteria or reference to measurements made observers also allocated each lung slice to one of four groups (O/O, p, q and r) which were assumed to correspond to the radiographic reading.

In 67% of cases readers of radiographs and lung slices agreed upon the type of opacity present. The pathological features of each lesion type were described and areas of disagreement examined.

Chronic Bronchial Suppuration and Inflammatory Bowel Disease

R. J. A. Butland, P. Cole, K. M. Citron and M. Turner-Warwick

Brompton Hospital and Cardiothoracic Institute, London

Seven patients with severe, unexplained, chronic bronchial suppuration and inflammatory bowel disease are reported. In three the rapidly progressive bronchiectasis developed within one year of proctocolectomy, in two it developed in association with an exacerbation of colitis and in the other two a milder, limited colitis post-dated the start of the lung disease.

The high incidence of arthropathies and skin rashes suggests a systemic disease and personal and family histories of autoimmune conditions were common. Antinuclear antibodies were detected in six of the seven and smooth muscle antibodies in five of the seven (in the absence of evidence of liver disease). Evidence of circulating immune complexes was found in two patients.

The four patients who received corticosteroid therapy had an impressive improvement in cough, sputum volume and dyspnoea, especially when on high doses.

Because of the time relationships of the bowel and lung symptoms, we suggest that these disorders may be related.

Lung Cancer: Current State of Treatment

S. G. Spiro

Brompton Hospital, London

Lung Cancer: Assessment of the Results of Chemotherapy

D. M. Geddes

Brompton Hospital, London

Chemotherapy, with Three Drugs, in the Treatment of Small-cell Carcinoma of the Bronchus

P. G. Harper, M. Dally, S. Guimaraes, S. G. Spiro, D. M. Geddes, J. F. Smyth, M. Hodson and R. L. Souhami

Brompton Hospital, London

A small proportion of patients with small-cell bronchogenic carcinoma survive for two years or more when treated with combination chemotherapy. Methotrexate is one of the most effective agents and can be given safely in high doses with folinic acid rescue. We have treated 70 patients, who were previously untreated, with methotrexate 200 mg/m^2 (24 hour infusion) followed by folinic acid rescue, cyclophosphamide 1 g/m^2, reduced to 750 mg/m^2 from Course 3, and CCNU 100 mg/m^2 on Courses 1 and 3 only. This was given every 21 days, depending on the blood count. Because of the recent reports of the effectiveness of VP16-213 (epipodophyllotoxin), all patients were treated with this agent on relapse, with a dose of 120 mg/m^2 on days 1, 3 and 5, every three weeks. As part of this study a comparison was made of the relative value of assessment of tumour mass by conventional methods (including chest radiograph, biochemistry and isotope scan with the information obtained from adding into the study CT scan of the thorax and abdomen).

32 male and 38 female patients, median age 62 years, were entered. There were no

exclusions. 44 (63%) had limited diseaes (confined to the hemithorax and supraclavicular fossa) and 26 (37%) had extensive disease. 54 patients (77%) responded to treatment, with a partial response (greater than 50% reduction in tumour size) in 38 (54%), reached at a median time of four weeks, and a complete response (disappearance of all tumour) in 16 patients (23%), reached at a median time of 10 weeks. 16 patients did not respond.

The first site of relapse was at the primary site alone in 35 patients (65%), distant alone in eight patients (15%) and generalized in 11 patients (20%). The brain was the first site of relapse in five patients (7%). Three patients are alive and tumour-free.

Median survival was 41 weeks. Patients with conventionally staged limited disease survived 42 weeks and with extensive disease 41 weeks. 10 patients remained free of disease for 18 months and three remain so at two years.

Despite widespread disease at diagnosis, relapse at the primary site, due to failure to eradicate bulk disease by chemotherapy alone, remains the major problem. This indicates the need for a randomized trial of the addition of radiotherapy to intensive chemotherapy, to see if better control of the primary site is possible. CT scanning contributed to the understanding of response in two ways. Firstly, it showed that with the limited disease category, judged by conventional staging, 93% had extensive disease. Secondly it identified a group of 10 patients (17%) with a small tumour mass, of whom 33% had a complete response to chemotherapy, and whose median survival was 64 weeks, compared with 42 weeks for the limited disease category judged by conventional staging.

Epipodophyllotoxin (VP-16/213) in Small-cell Carcinoma of the Bronchus Resistant to Initial Combined Chemotherapy

M. B. Dally, P. Harper, J. F. Smyth,
R. L. Souhami, D. M. Geddes and
S. G. Spiro

University College Hospital, London Chest Hospital, Brompton Hospital Collaborative Study Group

VP-16/213 has been shown to have considerable activity in the treatment of small-cell carcinoma of the bronchus and is a potent single agent drug. A partial response (decrease in tumour diameter of $>50\%$ of a clearly definable lesion) has been documented in up to 50% of cases in some studies. The ability of the drug to produce a second remission when the carcinoma becomes resistant to initial cytotoxic drugs has not previously been assessed. We have measured the response to three or more courses of VP-16/213 in 26 patients who showed either no initial response or became refractory to treatment with an initial three-drug regimen. This initial regimen (MCC) contains intravenous methotrexate 200 mg in 24 hours followed by folinic acid, intravenous cyclophosphamide 1 g/m^2 reduced after two courses to 0.75 g/m^2 given every three weeks: CCNU 100 mg/m^2 orally was given with courses 1 and 3 (MCC).

Twenty-six patients received VP-16/213 100 mg/m^2 intravenously or orally on days 1, 3 and 5 and then every 21 days. The treatment was well tolerated but seven patients had one course postponed by one week because of a total white cell count of <3000. Nine patients did not respond to MCC. The other 17 relapsed following either a complete (4) or partial (13) response. With VP-16/213 15 patients had disease progression or no improvement after three courses. Eleven showed either no improvement or a small improvement and received up to five courses before relapse or death. Only five patients had six courses before relapse. In total there was only one partial responder in 26 cases and no complete response. An additional 12 patients received less than three courses of VP-16/213 without any evidence of remission and died before three courses could be given.

These disappointing results suggest cross-resistance with at least one of the cytotoxic agents used in the initial treatment regimen.

Lung Cancer: Experimental Modes of Drug Sensitivity

A. Shorthouse and M. Peckham
Royal Marsden Hospital, Surrey

Lung Cancer: Future Studies

R. L. Souhami
University College Hospital, London

The Detection and Significance of Immune Complexes and Autoantibodies in Lung Cancer

K. Guy, A. Hunter, U. Dimario,
W. J. Irvine and N. W. Horne

MRC Clinical and Population Cytogenetics Unit, Edinburgh

The sera of newly diagnosed lung cancer patients and surgically treated lung cancer patients were examined for immune complexes and autoantibodies. Control subjects consisted of bronchitic patients and normal blood donors. Immune complex measurements were performed using four established and sensitive techniques (fluid and solid phase Clq assays, conglutinin binding assay and Raji cell radioimmunoassay) and a fifth newly devised technique based on the binding of immune complexes to *Staphylococcus aureus*. Using the first three techniques, which preferentially detect complement-binding immune complexes, only meagre quantities of complexes were found and in a maximum of 15% of newly diagnosed lung cancer patients. With the Raji cell assay and the *Staphylococcus aureus* binding assay, which appear to detect broader spectra of immune complexes, 44% and 33% of newly diagnosed lung cancer patients respectively were found to show evidence of complexes. However, bronchitic patients also appeared to have immune complexes at prevalence levels similar to those found in the sera of lung cancer patients. The presence of serum autoantibodies appeared to contribute to the finding of immune complexes in both cancer patients and control subjects. Nevertheless, preliminary experiments with the *Staphylococcus aureus* binding assay showed that immune complexes declined rapidly after tumour removal by surgery and suggest that this technique may potentially be a useful method for the monitoring of possible tumour recurrence after therapy.

Monoagent VP 16/213 in Advanced Lung Cancer and an Unsuspected Marrow Toxicity in Combination Chemotherapy

G. Anderson, Frances Bowyer and
L. Williams

Newport Chest Clinic

Forty-six patients with widely disseminated and histologically confirmed lung cancer were studied. There were 19 squamous carcinomas, 10 small-cell, six adenocarcinomas and 11 undifferentiated where the cell type was too malignant to allow precise classification. VP 16/213 was given in capsule form 100 mg twice daily for five days and cycles were given at 28-day intervals. A complete remission was recorded when all measurable lesions resolved for a minimum of six weeks. A partial remission when there was a decrease of more than 50% in the product of two perpendicular diameters of all measurable lesions for a minimum of six weeks.

Thirty-three patients survived a month to receive a second cycle and of these 11 (33%) showed a complete or partial remission. Activity was seen in all cell types. Responders survived a median of 34 weeks and non-responders 10 weeks. Toxicity was mild although all patients developed alopecia and only one showed leucopenia.

The effectiveness and safety of VP 16/213 as a single agent resulted in a similar study of the same dose of VP 16/213 combined with vincristine 2 mg and methotrexate 300 mg intravenously followed by generous folinic acid rescue. A single cycle of this combination caused profound pancytopenia in two of eight patients, one of whom died. Reduction of the methotrexate dose to 100 mg and extension of folinic acid rescue resulted in two of seven patients developing leucopenia and one died. A combination of VP 16/213 200 mg for five days, intravenous vincristine 2 mg and a very small dose of intravenous adriamycin (20 mg/m^2) caused leucopenia in one of six patients.

VP 16/213 is highly effective as a single agent but requires great caution in combination chemotherapy as it may produce an unexplained marrow toxicity.

Intrapleural Immunotherapy with Corynebacterium parvum in the Treatment of Recurrent Malignant Pleural Effusions

J. W. Millar, A. M. Hunter and
N. W. Horne

Chest Diseases Unit, City Hospital,
Edinburgh

Suppression of reaccumulation of pleural fluid can make a major contribution to the management of patients with disseminated cancer. Many methods of achieving this aim have been described, ranging from non-invasive chemical pleurodesis with a success rate of 50–70% to surgical pleurodesis. Intrapleural immunotherapy using *Corynebacterium parvum* has been successful in a few reported cases. We report our experience of a comparative randomized study of *C. parvum* versus the established agent mustine.

Twenty-one patients with proven recurrent malignant pleural effusions were randomly allocated to treatment groups receiving either *C. parvum* (7 mg) or mustine (20 mg) intrapleurally after aspiration. *C. parvum* (nine patients) proved superior to mustine (12 patients) in suppressing the reaccumulation of pleural fluid. In contrast to mustine, which was associated with marked nausea and vomiting in almost all patients, *C. parvum* was well tolerated with minimal side-effects. Three of the four patients who were deemed 'failures' after mustine therapy had complete suppression of pleural fluid reaccumulation following a single dose of *C. parvum*, the survival of the fourth being too short to assess response adequately. There were no 'failures' in the *C. parvum* group.

C. parvum is an effective, well tolerated agent in the management of recurrent pleural effusions. The relative contribution of the potent immunological stimulation it induces to its mode of action, however, remains uncertain.

Some Considerations of Hypertrophic Osteoarthropathy

L. DOYLE

Wythenshawe Hospital, Manchester

Although hypertrophic osteoarthropathy is associated predominantly with lung cancer, less frequent associations include tumorous and non-tumorous conditions in several other organs (larynx, oesophagus, heart, stomach, liver, diaphragm and bowel). There appears to be one common factor: the primarily diseased organ is innervated by one of two homologous nerves—the glossopharyngeal and the vagus. The vascular innervations by these two nerves and, in the case of lung cancer, the vascular changes which may be induced in the vicinity of these tumours were described. An attempt was made to integrate the known inexplicable facts relating to hypertrophic osteoarthropathy into one hypothesis.

Lung Cancer—Still a Surgical Disease

R. J. M. MCCORMACK

City Hospital, Edinburgh

Surgical excision remains today the form of treatment most likely to produce cure in a patient with lung cancer. When cases are diagnosed early, a 50% or better five-year survival has been reported. It has become popular in recent years to decry the use of surgery in small-cell tumours, but we know that a worth-while cure rate can be obtained by surgery even in these, admittedly less favourable, tumours. No patient has yet been cured of lung cancer by chemotherapy—although temporary regression is well documented. Figures from personal experience and from the literature were offered in support of this creed.

In Vitro Evidence of H_2 Receptors in Human Bronchus and Their Role in Allergic Bronchospasm

A. P. SMITH AND L. S. DUNLOP

Llandough Hospital, Penarth

Human bronchus obtained from pulmonary resection specimens was sensitized by incubation with human serum containing reagenic antibody against *Dermatophagoides pteronyssinus* and dose–response curves to histamine and the effects of antigen exposure in the presence of the H_1 receptor antagonist mepyramine and the H_2 antagonist metiamide were studied in vitro.

In the presence of mepyramine, the normal dose-related contraction caused by histamine was converted to a minor, but significant, dose-related relaxation, suggesting the presence of inhibitory H_2 receptors in human bronchus.

Metiamide abolished this effect of histamine, confirming that it was due to activation of bronchial H_2 receptors. Moreover, dose–response curves to histamine in the absence of mepyramine resulting in bronchoconstriction were potentiated by prior exposure of the muscle preparations to metiamide due to abolition of the weak inhibitory H_2 effect normally caused by histamine.

It was concluded that H_1 and H_2 receptors participate in the response of sensitized human bronchus to histamine, the H_1 effect being a powerful contraction and the H_2 effect being weakly inhibitory. Normally, in the absence of an H_1 antagonist, the H_1 effect is the more potent.

When the muscle preparations were challenged with antigen, vigorous contraction occurred. As this was partially inhibited by mepyramine, it was concluded that histamine contributed to the response. Metiamide had no effect, probably because the contraction observed was the maximum of which the preparation was capable. Submaximal antigen challenge produced a lesser degree of muscle contraction which was potentiated by metiamide, indicating that under those circumstances, too, inhibitory H_2 receptors participated in the bronchoconstrictor response.

H_1 and H_2 receptors therefore participate in histamine-induced and allergic bronchoconstriction, the effects of the H_1 receptor being predominant. H_2 receptors have a weak inhibitory effect and H_2 receptor antagonists potentiate the response to both histamine and antigen challenge in vitro.

Effects of H_2 Antagonists in Asthma

J. White, A. P. Smith, D. Leopold,
and J. Hartley

Llandough Hospital, Penarth

The demonstration of inhibitory H_2 receptors in animal and human bronchial muscle led to the hypothesis that H_2 receptor antagonists used in the treatment of gastrointestinal disorders might potentiate the effects of asthma. To investigate this possibility, cimetidine has been given to asthmatic volunteers in the following experiments.

1. A double-blind cross-over clinical trial comparing cimetidine 200 mg three times a day and 400 mg at night with placebo and chlorpheniramine.
2. The effects of inhaled cimetidine on inhalational dose–response curves to histamine.
3. The effect of cimetidine on the asthmatic response to exercise.

In none of these experiments was there any evidence that cimetidine potentiated the asthmatic response. It was concluded that cimetidine did not potentiate H_1 effects of histamine in asthmatic patients, possibly due to failure to achieve adequate tissue/receptor doses or possibly to a mixed H_1/H_2 effect of cimetidine itself. If further more potent H_2 antagonists are introduced, further experiments of this nature will be required.

The Effect of Anticholinergic and H_1 Receptor Blockade on Exercise-induced Asthma

J. P. R. Hartley, B. H. Davies and
S. G. Nogrady

Llandough Hospital, Penarth

There is evidence that the initial stimulus for exercise-induced asthma in susceptible individuals is airway cooling, but it is not known how this actually causes airway narrowing. Two possible pathways are through increased vagal activity and the effect of chemical mediators released from mast cells.

We performed two studies to find out more about vagal and mediator effects in exercise-induced asthma. In both studies, submaximal exercise was performed for eight minutes on a cycle ergometer on two occasions at each visit to the laboratory, with an interval of at least two hours between tests. The first test was performed without prior drug administration, while the second was preceded by inhalation of trial drug or placebo. These were given 90 minutes before exercise, single-blind and in random order. Exercise tests for each subject were closely matched in terms of oxygen uptake and ventilation.

In the first study, we compared the effect of the anticholinergic drug ipratropium bromide 0.1 mg and 1.0 mg with placebo. Ten subjects, mean age 32 years, were studied. Following the second exercise test, the mean falls in FEV_1 were 22.3%, 19.5% and 12.5% with placebo, 0.1 mg and 1.0 mg of ipratropium bromide respectively. Only the higher dose was significantly better than placebo in preventing exercise-induced asthma, although both doses produced the same degree of bronchodilatation. Using the initial exercise test each day for comparison, placebo and 0.1 mg and 1.0 mg of ipratropium bromide gave 23.6%, 37.7% and 64.6% protection respectively in terms of the fall in FEV_1 after exercise.

In the second study, the effect of the H_1 antihistamine clemastine fumarate, 0.5 mg given by inhalation, was compared with placebo using the same protocol. Ten subjects were studied, mean age 35 years. The mean falls in FEV_1 were 22.0% and 12.2% following exercise after placebo and clemastine respectively, and the difference was highly significant. Clemastine gave 47.7% protection from exercise-induced asthma in terms of FEV_1, compared with 15.2% following placebo in this study.

Metabolic Responses to Inhaled Salbutamol

R. D. H. MONIE, J. P. R. HARTLEY AND M. D. WINSON

Llandough Hospital, Penarth

Following prolonged usage of β adrenergic agonists, development of resistance (diminished responsiveness) has been demonstrated in normal subjects, not only in the airways, but also in the associated metabolic changes. In this study we demonstrate that resistance to the metabolic effects of inhaled salbutamol does occur in asthmatics in clinical practice and, following prolonged inhaled salbutamol, the results in normal subjects suggest that there is a tendency to develop resistance, although these results are not statistically significant.

Ten mild asthmatics, who were not on steroids, but required regular inhaled salbutamol, and ten normal subjects had an intravenous cannula inserted into a peripheral vein. Blood was taken for base-line measurements of glucose and potassium. From a Rota-haler, the participants inhaled 400, 800 or 1200 μg of salbutamol sulphate or placebo as a dry power in random order. The levels of blood sugar and plasma potassium were monitored at 15-minute intervals for 90 minutes following inhalation.

In the asthmatics the results showed no significant rise in glucose or fall in potassium following any of the doses of salbutamol. In the normal subjects there were significant changes in the rise of glucose and fall of potassium, and this was dose dependent.

The normal controls then inhaled salbutamol (400 μg four times a day) for two weeks and the glucose and potassium levels were monitored in a similar fashion following 1200 μg of salbutamol. These changes were then compared with the ones following 1200 μg of salbutamol prior to the two weeks of salbutamol inhalation, but the differences in the responses were not statistically significant.

Ipratropium Bromide by Nebulizer: A Pilot Study

R. W. PARRISH AND I. CAMPBELL

Llandough Hospital, Penarth

Ipratropium bromide has recently become available as an inhalant solution. In order to determine the optimum dose and time course of this preparation when given in nebulized form, we studied six hospital in-patients with differing types of airways obstruction. Three had asthma, two had chronic bronchitis and one had coalworkers' pneumoconiosis.

Each patient received each of three different doses, 0.1 mg, 0.5 mg and 1.0 mg, on consecutive days in random, single-blind order. No other bronchodilating substances were given during the test and observations were carried out for six hours after the dose. Side effects were not encountered.

There was no significant change in pulse rate or blood pressure in any patient at any dose of the drug. There was a significant improvement in FEV_1, FVC and PEFR after each dosage, but the effect did not vary significantly with the dose level.

Peak effect occurred approximately one hour after inhalation and a significant effect was still present at six hours.

0.1 mg given four to six hourly would appear to be a suitable dose regimen for ipratropium bromide when used in nebulized form.

Patterns of Recovery from Acute Severe Asthma

A. P. SMITH

Llandough Hospital, Penarth

Despite the frequency of admission to hospital for acute severe asthma, little is known about the natural history of the attack, nor have the various treatments proposed modified the mortality significantly over the last ten years. The rate of recovery in terms of improvement in peak flow rate from admission in a group of 41 patients admitted to hospital with acute severe asthma was studied. Three groups of patients were identified; 16 patients who recovered quickly from the attack; four patients whose recovery was slow and incomplete; and the remainder who were considered to demonstrate the usual rate of recovery from their attacks. Significant differences were found between the groups in the duration of hospital admission and the duration of intravenous treatment with bronchodilator drugs in the cases in whom this treatment was administered. 'Morning dipping' was a prominent feature of the accelerated and usual recovery groups, but was absent in the group that recovered slowly and incompletely, the latter comprising patients with complicated asthma most frequently associated with chronic bronchitis. Clinical and physiological differences between the groups on admission were few. Patients who recovered rapidly were younger and those who recovered slowly were older than the group considered to represent the usual rate of recovery and there were significantly more males in the accelerated group than in the other two groups. No significant differences in blood gases or pulse rate were noted between the three groups and pulsus paradoxus occurred equally in the groups described. Patients in the group recovering slowly had a significantly lower peak flow rate on admission than those of the other two groups in whom there was no significant difference in the peak flow rate on admission. The group of patients considered to represent the usual rate of recovery were more likely, however, to have a peak flow rate which was unrecordable on admission than those in the group which demonstrated an accelerated rate of recovery. When compared with all other patients, those with an unrecordable peak flow rate on admission were found to be slightly but significantly, more hypoxic than the others, but no significant differences were found in other physiological or clinical parameters. It appeared that patients belonging to the accelerated recovery group were less likely to have suffered from a coryzal illness or purulent bronchitis in the period immediately preceding the acute severe attack of asthma than the other two groups. Despite the fact that the blood gases on admission in the usual and accelerated rate of recovery groups were similar, patients who recovered rapidly were more likely to hyperventilate in a manner out of proportion to their peak flow rate resulting in a highly significant negative correlation between $P\text{CO}_2$ and peak flow rate. The results draw attention to differences in the way in which patients recover from attacks of acute severe asthma although it is difficult on the basis of this retrospective survey to predict confidently, at the time of admission, which patients will recover rapidly and which will not. The results do suggest, however, that the current 'massive' approach to treatment of acute severe asthma could be modified when more is known about the natural history of the attack.

The Place and Efficacy of Treatment in Pulmonary Infections Due to Mycobacterium avium-intracellulare

A. M. Hunter, A. P. Smith,
I. A. Campbell and P. A. Jenkins

Llandough Hospital, Penarth, and Public
Health Laboratory Mycobacterium
Reference Unit, Cardiff

Pulmonary infections by mycobacteria of the *avium-intracellulare* group are uncommon. Although these organisms may sometimes appear to be commensal, they are more frequently associated with significant pulmonary disease. In vitro testing of sensitivity to antituberculous drugs reveals a high degree of resistance and previous reports have suggested a poor response to standard antituberculous chemotherapy. Some have therefore advocated a multi-drug approach, reporting improved response rates.

In the past decade the Mycobacterium Reference Unit in Cardiff have isolated mycobacteria of the *avium-intracellulare* group in 95 cases in England and Wales. We have reviewed 68 of these cases, reviewing the natural history, clinical picture, radiographic pattern and the response to therapy. A surprisingly large number have responded to good standard antituberculous chemotherapy given for sufficient time.

Investigation of an Outbreak of Humidifier Fever in a Hospital Operating Theatre

A. Cockcroft, J. Edwards and
I. Campbell

Llandough Hospital, Penarth

Humidifier fever presents as a flu-like illness after exposure to antigens which are produced in the water tanks of re-cycling type humidifiers. It has been reported in offices and factories and we have recently investigated an outbreak in a hospital operating theatre.

We studied 60 theatre staff with serological tests, pulmonary function tests, chest radiology, skin tests, a questionnaire on symptoms and a clinical interview. Pulmonary function tests and chest radiographs were repeated three months after the humidifier was switched off. We also investigated a control group of 60 other hospital staff, matched for age, sex and smoking habits. Eight subjects, including two non-exposed controls, took part in inhalation challenge tests with humidifier water.

There was a significant relationship between a history of attacks of humidifier fever and positive serological tests, although many people with positive serology were asymptomatic. Positive immediate skin reactions to intradermal humidifier water occurred in people with strongly positive serology. Pulmonary function tests and chest radiographs were normal on both occasions, except in a few cases with pre-existing chest conditions.

Inhalation challenge reproduced an episode of humidifier fever after about eight to ten hours in four of the previously exposed subjects, including one who had negative serology and had not previously had any symptoms. The major features of the induced attacks were systemic, with fever, arthralgia, headache and discomfort on deep inspiration. There was a fall in vital capacity without evidence of airways obstruction or any change in gas transfer factor.

Studies on the Aerobiology of Grass Pollen, Skin Test Reactions and Desensitization in Hay Fever with Limited Extract Vaccines

J. Mullins, E. J. Parr and B. H. Davies

Sully Hospital, South Glamorgan

Atmospheric grass pollen concentrations were measured over a five-year period when the daily grass pollen concentration exceeded 100/m^3. Pollen concentrations rose from a morning minimum to an evening maximum, falling gradually during the night. Metereological conditions play an important part in determining pollen concentrations.

Of 77 patients skin tested with specific grass extracts, 26 hay fever patients (15 with asthma) received hyposensitization either with an extract of the grass pollen which gave the largest prick test reaction or with an extract of two grasses when there was no difference in reactions. Of 15 patients receiving the dual extract, nine reported improvement; of 11 patients receiving one extract vaccines, eight reported improvement. It is suggested that desensitizing vaccines of grass pollen could be simplified with little loss in efficacy.

Long-Term Acetylcysteine in Chronic Bronchitis: Pointers from a Randomized Multi-centre Trial

Vittorio Ferrari

Zembon Pharmaceuticals, Milan

In a double-blind trial, acetylcysteine (400 mg/day orally) was compared with a placebo in 744 patients with simple hypersecretory chronic bronchitis studied at 36 centres. 254 of 371 acetylcysteine patients and 241 of 373 placebo patients completed the planned six-month treatment; the remaining patients defaulted mainly for reasons unrelated to treatment after completing two to five months.

Monthly scores for sputum (quantity, purulence and thickness), difficulty of expectoration and cough severity decreased significantly more on acetylcysteine than on placebo. Monthly total incidence rates for exacerbations declined little from the first to the sixth month on placebo, in contrast to a four-fold decrease on acetylcysteine. Physician's and patient's assessments of effectiveness were significantly in favour of acetylcysteine. Life table methods allowed partial follow-ups to be incorporated into a coherent analysis, which showed the cumulative exacerbation-free rate to be 22.8% for placebo *vs.* 52.8% for acetylcysteine ($P < 0.001$). Making proper use of partial follow-ups is a more general problem in long-term trials and some protocol requirements for use of life tables were pointed out. The mechanism by which prolonged acetylcysteine apparently reduced initiation of acute recurrences was discussed both in the light of known relationships between hypersecretion and exacerbations in chronic bronchitis and in view of a possible enhancement by acetylcysteine of certain aspects of lung defence related to intracellular glutathione levels.

Antibody Responses and Clinical Reactions to Admune Influenza Vaccine in Healthy Non-smokers and Cigarette Smokers and Patients with Chronic Bronchitis

G. K. Knowles, P. Taylor and
M. Turner-Warwick

Cardiothoracic Institute and
Brompton Hospital, London

Admune influenza vaccine (A_2/Victoria/3/75, A_2/New Jersey/8/76 and B/Hong Kong/8/73) was administered intramuscularly to 18 healthy non-smokers, 13 healthy cigarette smokers and 30 patients with chronic bronchitis. Serum, nasal secretion and sputum homologous haemagglutination inhibition (HI) antibody titres were measured over a three-month post-vaccination period. Clinical reactions to the vaccine were recorded during the week following inoculation.

Increases in antibody titre to all three influenza strains were observed in serum and nasal secretion in each group and in sputum in the majority of patients with chronic bronchitis. An inverse relationship was noted between pre-vaccination antibody titres and the rise in antibody titre after vaccination. When subjects with similar pre-vaccination antibody status were compared no significant differences in conversion rate (four-fold or greater increase in HI titre up to one month following vaccination) or geometric mean titre in serum and nasal secretion were found between the three groups. In the chronic bronchitics sputum and nasal secretion antibody responses were comparable. Antibody conversions in sputum and/or nasal secretion without simultaneous increase in serum antibody were observed in a significant proportion of individuals in each group. Antibody persisted for at least three months following vaccination in all groups. Clinical reactions to the vaccine were mild and well tolerated.

These results show that HI antibody is produced in serum, nasal secretion and sputum following administration of Admune influenza vaccine and persists for up to three months. No differences in response pattern were observed between the groups studied. There was no evidence to suggest that the sputum antibody titres in the chronic bronchitics were reduced as a possible result of damage to bronchial mucosa. The discordant conversion results in serum and secretions in some individuals are consistent with local production of antibody in response to circulating influenza antigen.

Ventilatory Response to Transient Hyperoxia in Head Injury Hyperventilation

A. G. Leitch, J. E. McLennan,
S. Balkenhol, R. L. McLaurin and
R. G. Loudon

City Hospital, Edinburgh

We have measured the ventilatory response to ten breaths of oxygen in seven patients with hyperventilation following head injury. Breathing air all patients were hypoxic (mean $P\text{A}O_2$ 8.15 ± 0.9 kPa (SD)) and hypocapnic (mean $P\text{a}CO_2$ 3.55 ± 0.8 kPa) with a respiratory alkalosis (mean pHa 7.53 ± 0.06). Following oxygen administration ventilation fell by 40.1 ± 12.7% from the mean control value of 16.06 ± 3.75 litres/minute BTPS to a minimum at 20.4 ± 2.9 seconds after the first breath of oxygen. The pattern of ventilatory response suggests a carotid-body-mediated reflex. The depression of ventilation following oxygen in these patients is significantly greater than that seen in other hypoxic subjects. Our findings suggest the hypothesis that hyperventilation in head injury is secondary to bilateral cerebral damage resulting in a decrease in cortical inhibitory influences on the medullary respiratory control centre. Our observations in head injury emphasize the need to consider central nervous system mechanisms in disorders of control of breathing.

Oral Prophylaxis of Exercise-induced Asthma: A Study of Two New Drugs

I. S. Petheram, C. W. Bierman, A. Cobley
and S. G. Spiro

Brompton Hospital, London

We have performed two studies to test whether oxatomide, an inhibitor of histamine release from most cells, and ketotifen, a phosphodiestase inhibitor and potent H_1-receptor antagonist, provide prophylaxis against exercise-induced bronchospasm. The drugs were studied separately. In each study 12 volunteers who experienced exercise-induced wheezing were tested on four separate occasions. Each subject took the trial preparation two hours before running. In the first study oxatomide 10 mg, 30 mg or 60 mg or placebo were taken in random order and in the second ketotifen 1 mg, 2 mg or 4 mg or placebo were taken similarly.

The subjects were exercised on a treadmill according to a standard protocol. Lung function measurements were made before and immediately after exercise and at 3, 5, 10, 15 and 20 minutes using a dry wedge spirometer attached to a microprocessor. Peak expiratory flow rate (PEFR), forced expired volume in one second (FEV_1), forced vital capacity (FVC) and forced expiratory flow at mid-vital capacity (V_{50}) were obtained from a forced vital capacity manoeuvre at each time point.

There was no significant difference between group mean PEFR, FEV_1, FVC or V_{50} before any of the four exercise tests of the oxatomide or ketotifen studies. After exercise there was no significant difference in the time or degree of maximum fall of mean values with any dose of ketotifen or oxatomide compared with placebo. In one of 12 subjects ketotifen seemed to protect from the development of exercise-induced bronchospasm.

Carbon Monoxide and Walking Distance in Chronic Bronchitis and Emphysema

P. M. A. Calverley, L. McElderry,
R. J. E. Leggett and D. C. Flenley

University of Edinburgh

Carbon monoxide reduces the maximal oxygen uptake achieved by normal people and the maximum exercise time in bronchitic patients. Since persistently raised values of carboxyhaemoglobin are seen in chronic cigarette smokers, this may be contributing to some of the disability experienced by those with chronic bronchitis. We have studied 15 patients with severe chronic bronchitis (mean FEV 0.5 ± 0.2 litres, mean FVC 1.6 ± 0.4 litres) using the distance walked in 12 minutes to assess exercise tolerance. Each subject attended on two occasions and walked while breathing air and subsequently while breathing oxygen, before and after inhaling sufficient carbon monoxide to increase the venous carboxyhaemoglobin level by 9% above the initial value. Venous blood was taken for the estimation of the oxygen tension at 50% saturation (P50), 2.3 DPG and COHb levels. Arterial oxygen saturation was measured non-invasively by ear oximetry before and immediately after each walk in eight of the subjects. These measurements allowed us to estimate the oxygenation of venous blood from the leg muscles ($P\text{v}O_2$) assuming an arteriovenous difference of 7 or 10 ml oxygen per 100 ml blood.

There was a significant reduction in the distance walked when the carboxyhaemoglobin level was increased, as compared to that when breathing air alone ($P < 0.01$), However. the reduction in exercise tolerance was abolished when the patient walked breathing oxygen. There was no significant relationship between the distance walked and the arterial oxygen saturation, but there was a significant relationship ($P < 0.01$) between the calculated value of $P\text{v}O_2$ assuming both 7 or 10 ml oxygen per 100 ml blood and the distance walked whatever gas mixture was used. Thus, carbon monoxide at levels often found in bronchitic patients who smoke cigarettes can reduce every-day exercise tolerance, presumably by interfering with the transport of oxygen to the muscles.

A Comparison of Fibreoptic Bronchoscope Transbronchial Lung Biopsy with Other Techniques in the Diagnosis of Sarcoidosis

D. M. Mitchell, D. N. Mitchell,
C. J. Emerson and J. V. Collins

Brompton Hospital, London

A diagnosis of sarcoidosis was made in a consecutive series of 79 patients of whom 24 presented with atypical features. Of 42 patients having transbronchial lung biopsy 37 (88%) were found to have epithelioid and giant cell granulomas in lung tissue, thus supporting the diagnosis. Of 22 patients 17 (77%) had positive bronchial mucosal histology. Kveim tests were completed in 44 and 19 (43%) were positive, 11 equivocal and 14 negative. In 16 patients histological support was obtained by biopsy of a variety of other tissues. The clinical presentation and degree of histological support provided by the various procedures in reaching a diagnosis of sarcoidosis was discussed. Transbronchial lung biopsy provides a higher diagnostic yield for sarcoidosis than any other method in this group of patients.

Lung Disease in Marfan's Syndrome

D. Bellamy, J. R. Wood, Ann Child,
D. Denison and K. M. Citron

Brompton Hospital, London

Marfan's syndrome is an inherited disorder of connective tissue manifesting mainly as abnormalities in the eye, cardiovascular and skeletal systems. There have been few reports in the literature of an association with pulmonary abnormalities.

We have examined the case notes and chest radiographs of 60 patients with Marfan's syndrome with particular reference to lung disease. The population studied represents all the available patients from four London teaching hospitals, presenting to a variety of medical and surgical disciplines but mainly for skeletal or cardiac complaints and a few with respiratory symptoms. The majority of patients had normal lungs radiographically and no respiratory symptoms. Observed pulmonary abnormalities included cystic lung disease, emphysema, spontaneous pneumothorax and aspergilloma. This series also contains a high proportion of patients with skeletal deformities of the chest and spine who subsequently have developed secondary defects of pulmonary function. The diagnosis of Marfan's syndrome is often difficult in the less classical forms and new methods for diagnosis were discussed.

The Frequency of Double Primary Tumours in Surgical Resection for Carcinoma of the Bronchus

D. Lamb

University of Edinburgh

572 sequential resections (306 pneumonectomies and 266 lobectomies) were examined over a three-year period. All specimens were fixed by inflation with formal saline and cut into 1 cm sagittal slices. Using the criteria of Warren and Gates five definite and several possible double primary tumours were identified. None of the patients had been clinically thought before operation to have two tumours. The ability to identify small second tumours was in part due to the method of examing the resected specimen.

BTA Study of Beclomethasone Dipropionate plus Salbutamol

A. D. Mackay and A. J. Dyson

A bronchodilator inhaler is often used before inhalation of a corticosteroid in an attempt to improve the efficacy of the latter in asthma. The BTA has carried out a study to test this concept.

The study was a multi-centre, double-blind within-patient comparison of two regimens given in random order each for three months:

1. Regular beclomethasone dipropionate preceded by regular salbutamol, i.e. salbutamol–BDP.
2. Regular beclomethasone dipropronate followed by regular salbutamol, i.e. BDP–salbutamol. Patients received two metered doses of each drug (i.e. beclomethasone 100 μg and salbutamol 200 μg) four times daily. An additional salbutamol inhaler could be used as necessary for symptomatic relief. Patients kept daily diary cards recording symptoms, additional salbutamol inhaler usage and two PEFR readings twice daily.

Sixty patients (mean age 48 years) were recruited from ten centres. All had an FEV_1 above 40% predicted, a greater than 20% improvement in FEV_1 after inhaled bronchodilator or a greater than 20% lability in PEFR during one week, and had previously shown an objective improvement with a course of corticosteroids. Patients taking regular corticosteroid tablets were not eligible. There were 12 withdrawals. Ten were unrelated to the trial treatment. One patient withdrew on the salbutamol–BDP regimen because of an exacerbation of asthma requiring corticosteroid tablets for more than ten days and one withdrew on the BDP–salbutamol regimen because of oesophagitis and oral candidiasis.

Of the remaining 48, 12 patients were not included in subsequent analysis as they required courses of corticosteroid tablets for exacerbations of their asthma. Four had exacerbations on the salbutamol–BDP regimen only and two had exacerbations on the BDP–salbutamol regimen only. Six patients had exacerbations on both regimens. 36 patients therefore remained for analysis, which was based on the last two months of each treatment period to reduce the possibility of a carry-over effect from one period to another.

The results do not support the concept that regular beclomethasone dipropionate is more effective when preceded by salbutamol in asthmatic patients who have been shown to respond to treatment with corticosteroids. Control was similar during regular treatment with both drugs irrespective of the order in which they were given.

FUTURE MEETINGS OF THE BTA

The list below gives details of future meetings, both arranged and provisionally planned. I hope this will prevent the clashing of dates with meetings arranged by other Societies.

2–8 September 1980	Jointly with the Norwegian Thoracic Society, Lillehammer, Nr. Oslo, Norway. The availability of cheap air fares for a longer stay abroad has caused the BTA to amend the dates of this meeting. These are correct at the time of going to press.
29–30 January 1981	Jointly with the Thoracic Society, Royal Free Hospital, London. A two-day meeting.
6–9 May 1981	Jointly with the Europe Region International Union Against Tuberculosis and the Chest, Heart and Stroke Association, Bournemouth.
28–29 January 1982	Jointly with the Thoracic Society. A two-day meeting at the Royal Free Hospital, London.
30 June–3 July 1982	Jointly with the Thoracic Society, University of York.
27–30 June 1983	Jointly with the Thoracic Society, Churchill College, Cambridge.
24–27 June 1985	Churchill College, Cambridge.

Further details of these meetings can be obtained from Dr G. Anderson, Newport Chest Clinic, 129 Stow Hill, Newport, Gwent NPT 4GA.

FUTURE MEETINGS OF THORACIC SOCIETY

29–30 January 1981	Jointly with the BTA. A two-day meeting at the Royal Free Hospital, London.
4–5 July 1981	Jointly with Scottish Thoracic Society. St Andrews University.
28–29 January 1982	Jointly with the BTA. A two-day meeting at the Royal Free Hospital, London.
30 June–3 July 1982	Jointly with the BTA. University of York.
27–30 June 1983	Jointly with the BTA. Churchill College, Cambridge.

BOOK REVIEWS

Management of the Patient–Ventilator System: A Team Approach

Kathren V. Martz, Jerry Joiner and Ridger M. Shepherd

St Louis: C. V. Mosby. 1979. Pp. xvi+254. Price not stated

This book is directed to physicians, nurses and respiratory therapists responsible for the moment-to-moment care of patients requiring mechanical ventilation. It contains a wealth of common sense, reflects what must undoubtedly be the extensive experience of the authors and includes a particularly good chapter on patient comfort, both physical and psychological. The approach is practical rather than theoretical and the very detailed instructions which are given for the preparation and execution of some common procedures may well be of value to nursing staff newly exposed to this type of work. However, those seeking a clear understanding of the ventilatory requirements of different types of respiratory insufficiency will be disappointed: for example, there is no discussion of the management of severe acute asthma and, apart from the presence of compensated respiratory failure in patients with chronic obstructive airways disease, there is little account of the special features of patients with type of disorder. Similarly, the classification of ventilators into pressure- or volume-cycled is over simplified and not entirely accurate, and the description and illustration of continuous positive airway pressure as 'positive end expiratory pressure with spontaneously initiated breaths' is misleading. Several of the ventilators which are described in detail are used less commonly in Great Britain than in the United States.

The book is intended as a practical manual but the pages are awkwardly large (22 × 28 cm), some are specially marked for quick reference and all are perforated and punched for tearing out and separate filing—so woe betide the next reader! There is no index but the list of contents is excellent and the layout and typeface are clear. It is phraseology and presentation which are likely to prove the greatest drawback to an English reader: learning has been 'internalized', exercises are included as a 'learning experience' so that 'decisions can be arbitrated', and there is a section with the title 'ventilometrics'.

In summary then, this book reflects transatlantic differences in methods of teaching and learning rather than in patient management. As the authors state in the opening sentence of their preface 'Offering yet another book on the management of the patient–ventilator system is a bit like selling sand at the seashore'. To conclude in the same style, this is good quality sand but the reviewer found the packaging unattractive.

M. Branthwaite

Blades' Surgical Diseases of the Chest

Donald Brian Effler

St Louis: C. V. Mosby (London: YB Medical Publishers Ltd). 4th edition. 1979. Pp. xvi+839. Price £41

This textbook could and should be one of the best reference books on cardiothoracic surgery that is available today. The editor heads a team of contributors each of whom is a world renowned authority. The book fails, however, to live up to this expectation. It is large and contains an introductory chapter on medical ethics, the omission of which would not detract from the book, and to find similar chapters in other surgical textbooks would become tedious.

For review purposes the book can be divided into three main sections: thoracic surgery, cardiac surgery and a miscellany of pacing, anaesthesia and cardiac assist devices.

The thoracic surgical sections, about one-third of the book, are the most disappointing. There is a tendency for overlap between chapters and in one chapter factual detail is almost absent. The reviewer has the impression, indeed it is stated in the Preface, that there has been little change in thoracic surgical practice in the last decade, so it is not necessary to bring these chapters up to date. The late Dr Blades was regrettably too ill to alter Chapter 4 and it has been reprinted in its entirety. This chapter is entitled 'Pulmonary Suppurations, Empyema, Bronchiectasis and Lung Abscess', but contains a large section on pleural tumours and tumours of the lung, covering such important topics as extrapulmonary manifestations of lung cancer. The next chapter, obviously newly written, is entitled Pulmonary Neoplasm, Malignant and Benign in which the whole concept of lung tumours is admirably covered but surely it should contain the appropriate sections from the previous chapter.

The photomicrographs in black and white do not mean a great deal to the uninitiated pathologist and many of the chest radiographs are not of great clarity.

There is, of course, a chapter on the oesophagus in which the vexed problem of reflux oesophagitis receives no more than two pages and nowhere in the index is 'hiatal hernia' or similar title even mentioned.

The second section of the book dealing with cardiovascular surgery is much more professional and has been brought right up to date by its many authors. Initial chapters are extracorporeal circulation, blood and its storage, and a short section on cardiopulmonary resuscitation. Later in the book are excellent chapters covering 'myocardial preservation' techniques and anaesthesia for cardiovascular surgery.

The operative detail on both congenital and acquired heart disease is accompanied by diagrams some of which are crystal clear, but others—particularly pertaining to Fallot's tetralogy—are not satisfactory.

Two chapters on myocardial revascularization are included which repeat each other and one could easily be excluded without detriment to the text as a whole. The final chapters in the third arbitrary section very properly cover pacemaker implantation, cardiac assist devices and heart transplantation.

The book can be recommended to surgeons training in cardiothoracic surgery and this edition should be available in libraries of the larger hospitals. The cost has not increased greatly compared with the third edition but no doubt will rise with future editions. To keep the cost down or to justify such increases as will follow, careful editing and omission of duplication is essential.

The chapters on pulmonary and oesophageal surgery require rewriting to bring the fifth edition up to the standard that Dr Blades would have expected from his textbook.

B. A. Ross

Asthma—The Facts

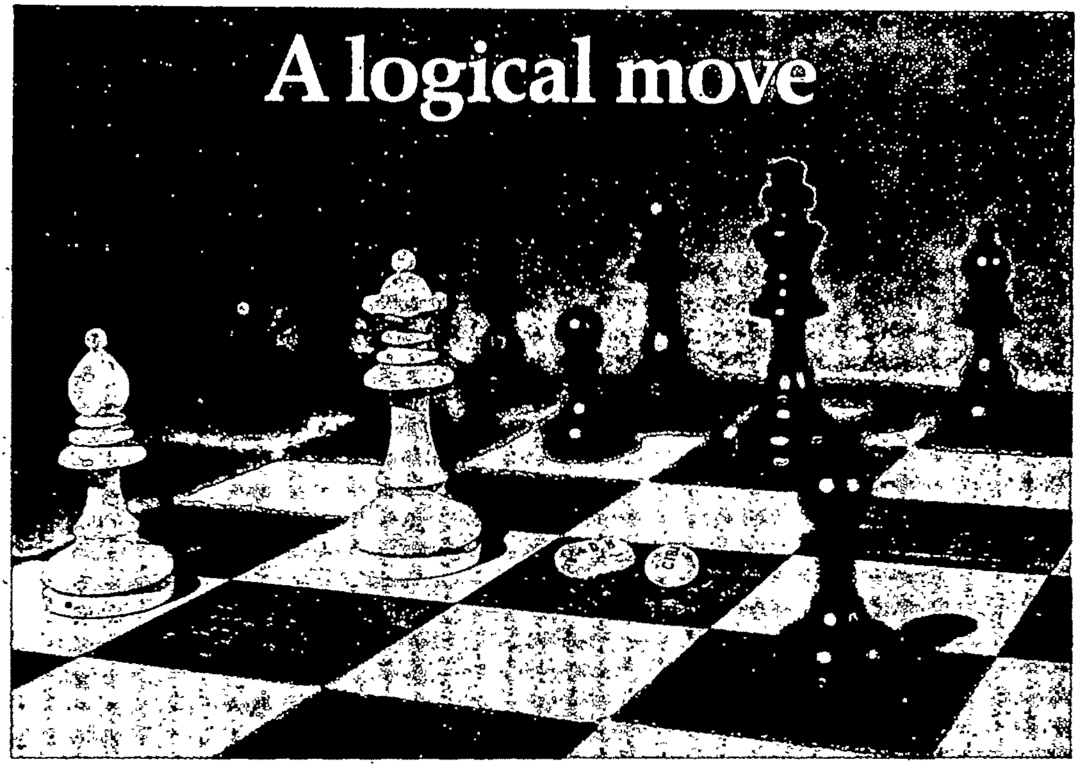
Donald J. Lane and Anthony Storr

Oxford: Oxford University Press. 1979. PP. vii + 163. Price £4.50

As a theoretical physicist who has been struck by asthma in early middle age, I find this book doubly interesting. As a patient, I can compare my symptoms with those of others (and find that I could be very much worse), and I can satisfy my more detached scientific curiosity to learn what is known about this strange widespread and distressing condition.

Although the book is an Oxford Medical Publication, it is intended for both medical and non-medical people. To begin with, there is an introduction by Dr Storr, a psychiatrist, who tells of his experience of asthma as a patient. His contribution is non-technical and very readable. The main part of the book is by Dr Lane, a chest physician; this is more scientific and the language is more formal. I would guess that it is quite accessible to almost any patient, given a reasonable amount of persistence, though some people may be put off before they see graphs scattered through the pages. Some technical terms are used, but they are explained when they are introduced, and one can refer back to the explanations through the index when one forgets them. The index could be a bit fuller; for example, the many people who rely on Intal will be surprised not to see it listed—though perhaps if I used it myself I might know that I should look under DSCG, and I should then find that it is discussed towards the end of the book.

Peter Landshoff
Christ's College, Cambridge



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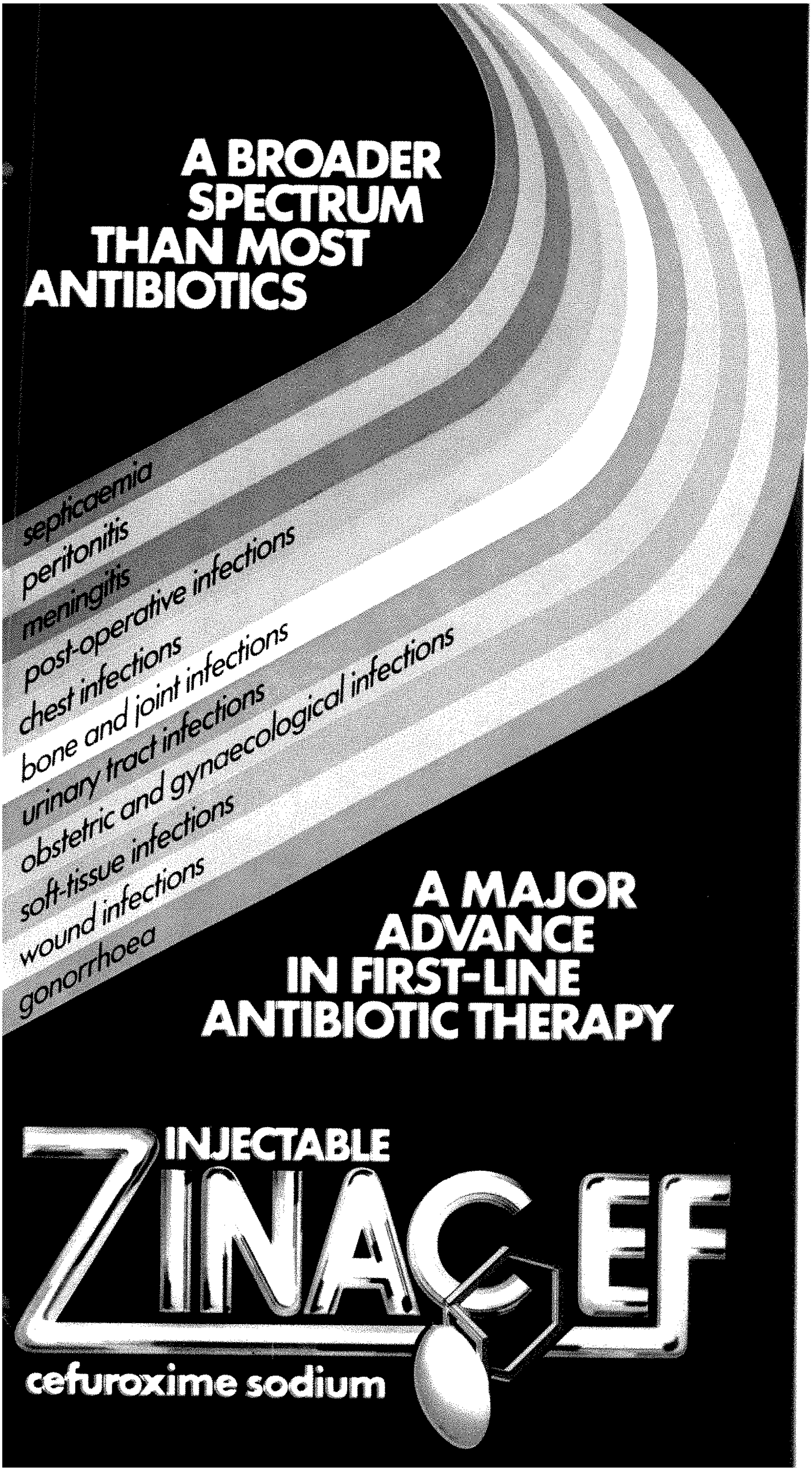
A BROADER SPECTRUM THAN MOST ANTIBIOTICS
septicaemia
peritonitis
meningitis
post-operative infections
chest infections
bone and joint infections
urinary tract infections
obstetric and gynaecological infections
soft-tissue infections
wound infections
gonorrhoea
A MAJOR ADVANCE IN FIRST-LINE ANTIBIOTIC THERAPY
INJECTABLE
ZINACEF
cefuroxime sodium

Prescribing informati
*

Indications
Serious bacterial infections, esp
where the causative organisms
not yet been identified

Conditions include
Chest infections
Septicaemia
Soft tissue infections
Obstetric and gynaecological infections
Bone and joint infections
Ear, nose and throat infections
Meningitis
Gonorrhoea

Dosage
Adults Generally 750mg t d s. i
i v Severe infections 1 5 grams t
i v Frequency of injections can b
increased to six hourly if necess
giving total doses of 3 grams to 6
grams daily
Infants and children 30 to 100m
day in three or four divided dose
60mg/kg/day will be appropriat
most infections

Neonates 30 to 100mg/kg/day
two or three divided doses

Gonorrhoea Single dose of 1 5
(2 x 750mg i m into different site

Contra-indications
Hypersensitivity to cephalospori

Precautions*
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Review Article

SMOKING BEHAVIOUR: A PSYCHOLOGY OF THE CIGARETTE HABIT

R. Stepney

Addenbrooke's Hospital, Cambridge

The persistence of tobacco smoking in the face of often rigorous proscription and, in our own time, despite agreed severe health hazards is a remarkable phenomenon which has not yet been satisfactorily explained. Cigarette smoking is by far the most common form of tobacco consumption and is also the form most closely and clearly associated with disease. The most pressing need in terms of preventive social medicine is therefore for a fuller understanding of the factors which initiate, develop and maintain the cigarette smoking habit.

This review is concerned primarily with the presentation of two approaches to the problem of smoking motivation. One view considers smoking as addiction; the other sees reasons for continued smoking in the usefulness of cigarettes in the control of arousal and the manipulation of psychological state. This is preceded by a brief history of tobacco use, an account of the current prevalence of smoking and of possible non-pharmacological sources of reward and an assessment of the role of nicotine in the cigarette habit.

History of Tobacco Smoking

A legend amongst the Huron Indians of North America tells how the Great Spirit sent a naked girl to restore a land ravaged by famine. Potatoes grew where she touched the ground with her right hand, corn where she placed her left hand, and, from where she sat down, sprang tobacco. Whatever the origins of the tobacco plant, it is likely that the peculiarly pleasurable consequences of inhaling its smoke were discovered more or less by chance during the use of various plant materials in sacred rituals involving fire and incense (Corti 1931). The history of Western man's association with tobacco has a more clearly defined beginning in the discoveries of Columbus in October 1492 (Brooks 1953). Inhaling smoke was not unknown in the Old World; Europeans had inhaled the fumes of such unappetising substances as coltsfoot and dried cow dung for medicinal purposes, and Herodotus reported the use of hemp as an intoxicant by Scythian tribes. The use of tobacco, however, was a curious novelty. By the end of Elizabeth's reign, tobacco had gained a strong hold over England. King James I might inveigh against a habit 'loathsome to the eye, hateful to the nose, harmful to the brain, dangerous to the lungs, and in the black stinking fume thereof nearest resembling the horrible Stygian smoke of the pit that is bottomless', but few of his subjects agreed. Official opposition took a variety of forms. Murad the Cruel of Turkey (1623–40) had smokers beheaded, hung and quartered. In the Russia of the first Czar, Michael Feodorovitch Romanov, smokers were flogged and exiled to Siberia. In Japan in 1616 the penalties for smoking included imprisonment and the confiscation of property. Severe and immediate punishment, however, proved no more effective in halting smoking than current fears of long-term health consequences.

Later, however, governments came to tolerate and even encourage tobacco use, prompted in part by the realization that the commodity was an excellent source of revenue—derived either from customs dues or from the sale of monopolies to deal in tobacco goods.

In the course of its history the tobacco habit has undergone many transformations. The sixteenth and seventeenth centuries saw the ascendancy of the pipe, whilst in the eighteenth century snuffing tobacco powder became the favourite method and in the nineteenth century the cigar and the tobacco quid predominated. In 1881, however, the introduction of cigarette-making machines heralded the era of mass production. The convenience and low cost of this form of tobacco led to a massive growth in consumption and the development of milder tobaccos (derived from new strains of plant and new methods of leaf curing) encouraged inhalation.

CURRENT STATUS OF TOBACCO SMOKING

The total weight of all tobacco goods sold in the United Kingdom in 1975 was 245.7 million pounds (Lee 1976). Of this, 0.2% was in the form of snuff, 3% cigars and cigarillos, 4.5% pipe tobacco and 92.3% cigarettes, hand-rolled, plain and filter. In each of the past three years, 125 thousand million cigarettes have been smoked by the country's 18 million smokers, at an average rate of 19 per day. Roughly 45% of the adult male population and 43% of the female population smoke cigarettes though there are in fact slightly more female than male smokers. Over the past 30 years the proportion of male smokers has declined steadily from around 65% in 1948, whilst the proportion of women smoking has remained relatively stable (Capell 1978). However, whilst the sex difference has become less pronounced, a difference according to social class has emerged, the highest social class having the smallest proportion of smokers and the lowest class the largest.

Age also has a marked effect on smoking. Cigarette consumption is at its peak amongst men who, in 1975, were 50–54 years of age (Lee 1976, Table 14). This age group would have been in their late teens in 1939 and there is little doubt that the greater per capita consumption of cigarettes represents the persisting effect of the increase in smoking during the Second World War. Perhaps surprisingly, women show no corresponding peak at this point. Another interesting feature of the relationship between age and cigarette consumption is the markedly lower rate in those over 65 years of age. People in this age range will probably have smoked fewer cigarettes all through their lives, though the reduction in consumption may also reflect a genuine lessening of interest in smoking. The percentage of ex-smokers increases markedly in the male over-60 age group and anecdotal evidence suggests that older people are often able to give up smoking without too much difficulty. Increased mortality amongst the heaviest smokers may also have played a part in reducing per capita consumption in the elderly.

In absolute terms, the past 20 years have seen virtually no change in the total number of people smoking manufactured cigarettes. Over the same period, however, sales of cigarettes have risen and smokers are therefore, on average, smoking more heavily.

Between 1949 and 1976, average consumption by male smokers rose from approximately 100 to 150 cigarettes per week and, in women smokers, from 50 to 120 cigarettes per week. The increase in the number of cigarettes consumed by each smoker has occurred over a period during which the average tar and nicotine yield of cigarettes has decreased considerably. The declining yield of the cigarettes smoked has been due mainly to the almost complete switch from high-yielding untipped cigarettes to lower-yielding filter brands, although the delivery of both plain and filter cigarettes is also being progressively reduced and the introduction of low-tar brands over the past seven years has made some contribution. In 1978, plain cigarettes accounted for under 10% of total sales, whilst the six best-selling low-tar brands accounted for 11% of the market. It would be interesting to know whether those who have followed the government's advice and successfully made the switch to low-tar brands are representative of smokers in general or whether they constitute an atypical subgroup. Many smokers have tried low-tar brands, found them unpleasant or 'unsatisfying' and returned to a higher delivery cigarette, which would suggest that the strategy of reducing cigarette yields and persuading smokers to switch to lower delivery brands might be of only limited value.

The many different forms which smoking takes and the complexity of the smoking act itself make any unitary explanation of the behaviour difficult. It is likely that the different forms of smoking involve rewards derived in differing degrees from social, sensorimotor and pharmacological sources. Sensorimotor rewards would seem to be particularly important in pipe smoking, for example, where the rubbing of the tobacco and the filling of the pipe and its subsequent cleaning seem as important a part of the procedure as the act of drawing smoke itself. Just as in the case of pipe smoking, with its homely and academic associations, the image of affluence and success attached in our society to the smoking of cigars is probably an important part of the motivation.

If different sources of reward are likely to operate according to the particular *form* of smoking practised, it is equally true that different factors operate at the various stages in the *development* of the habit. This is most clearly so in the case of cigarette smoking, where the complex interplay of positive and negative factors of diminishing and increasing importance is perhaps best represented diagrammatically (Fig. 1).

SOCIAL FACTORS: PICKING UP THE HABIT

There is strong evidence that starting to smoke is related to social factors, particularly the influence of parents and peer group, and to the 'anticipation of adulthood' (Mausner & Platt 1971; Russell 1971). A survey of over 1500 adolescents carried out in 1969 on behalf of the American Cancer Society showed that the median age of first experimentation with cigarettes was 12 years, identifying the time around puberty as the critical point for initiating the habit. 32% of the teenage children of mothers who smoked were cigarette smokers compared with only 23% of the children of non-smoking mothers. Having a father who smoked influenced teenage smoking to a similar extent, but the importance of having an elder brother or sister who smoked was even greater. Smoking was found in only 20% of teenagers whose elder brothers or sisters did *not* smoke, but in 43% of teenagers whose older siblings smoked. Of greatest influence, however, was whether or not one's friends smoked. 56% of smokers and only 14% of non-smokers said their friends smoked. The teenagers interviewed thought, on average, that 72% of

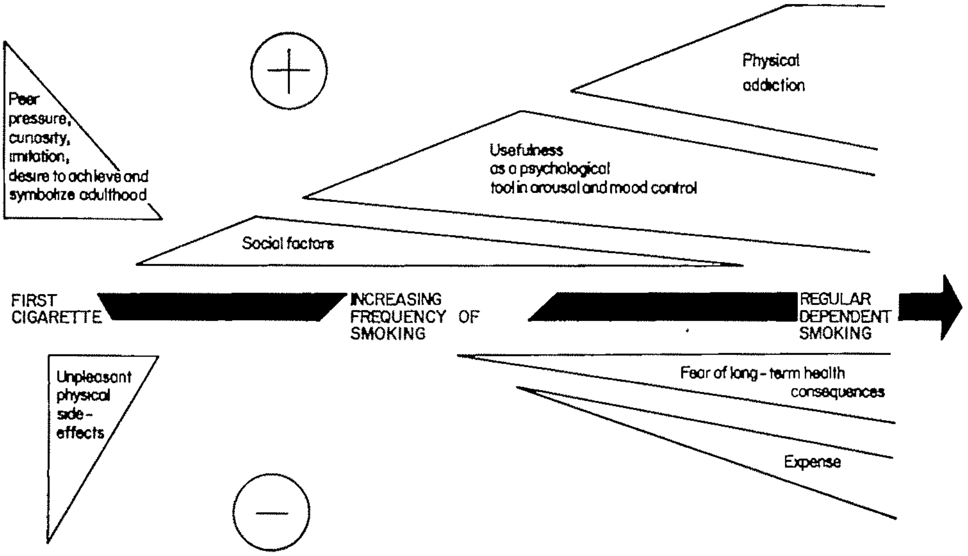
+
Peer pressure, curiosity, imitation, desire to achieve and symbolize adulthood
Physical addiction
Usefulness as a psychological tool in arousal and mood control
Social factors
FIRST CIGARETTE
INCREASING FREQUENCY OF SMOKING
REGULAR DEPENDENT SMOKING
Unpleasant physical side-effects
Fear of long-term health consequences
Expense
−

Fig. 1. Factors affecting the different stages of the cigarette smoking habit

adults smoked (when the true percentage was little over 40%), providing a clear indication of the extent to which smoking and adulthood were associated in the children's minds. The effect of the behaviour of parents, peers and siblings on childhood smoking is presumably mediated partly through increased exposure to cigarettes and partly through imitation and example. However, individual differences in personality—and particularly in orientation towards the kind of psychological rewards offered by smoking—must also be relevant. McArthur et al. (1958) quote the following passage from a study which investigated smoking in a typical American high school: 'Law and the mores deny high school students the right to enjoy the pleasures derived from tobacco, gambling and alcohol. However, the mystery with which adults surround these areas of behaviour lends them a special value which seems to act as a stimulus to many young people who desire to experience the supposed thrill of pleasures their elders deny them.' Transgressing the restrictions imposed by law and taboo is a source of excitement, both individually and within the clique of the initiated. This kind of excitement, of course, does not appeal to all adolescents. Not surprisingly, those to whom it does appeal are also more likely to indulge in other risk-taking behaviours and to find other sources of conflict with authority. In their review of smoking in childhood, Mausner and Platt (1971) present evidence that those boys and girls who begin to smoke 'are more rebellious than non-smokers, have poor relations with authority figures, date frequently, drive early and use alcohol, and tend to have accidents when they drive.' Russell (1971) reviews a number of studies of the onset of smoking in English adolescents and identifies similar factors.

Both English and American studies have shown that early smoking is related to lower levels of perceived (and real) academic achievement. Russell (1971) accounts for this association by suggesting that children who perform poorly at school compensate by finding status outside school in the company of those older than themselves. At this stage, the image of the smoker as mature, tough and sophisticated is undoubtedly attractive. In addition, the smoker is likely to find that smoking is a useful accomplishment, especially in difficult social situations. It provides something to do with the hands and the giving and receiving of cigarettes helps to establish new friendships and improves the cohesiveness of a social group. These factors can be expected to be important at a critical period in an adolescent's development of personal relationships, especially those involving the opposite sex.

The importance of the image of the smoker, and the supposed social usefulness of smoking does not end with adolescence. There is evidence that adults continue to regard smoking as indicative of favourable personality traits. In a study by Weir (cited in Mausner and Platt 1971), subjects were shown a series of photographs in some of which people were portrayed smoking whilst in others the cigarette had been removed by retouching. Subjects were asked to characterize the person portrayed by choosing adjectives from a list. The presence of the cigarette produced a marked increase in the choice of adjectives such as adventurous, rugged, daring, energetic and individualistic, and a decrease in the use of the terms awkward, timid, shy, gentle and quiet. In a further study, 200 female students were asked to choose people with whom they would like to spend time in three different kinds of activity, social, university and work. There was a strong tendency for smokers to choose the company of other smokers and for non-smokers to choose to be with non-smokers, even though the individuals chosen for each activity were different. The importance of smoking in defining self-image is also great. The majority of adult smokers think that a photograph of themselves without a cigarette would not show 'the real me', whilst a picture of them with a cigarette would. The influence of family and friends, of the cultural stereotype of 'the smoker', and of the social rewards of smoking seem therefore to be of great importance in initiating the habit and of continuing importance in maintaining it.

SENSORY ASPECTS AND THE PSYCHOANALYTIC VIEW

Taste and smell have received relatively little consideration as factors influencing smoking, although Brill (1922) argued a strong case for their importance, suggesting that the great variety of available experience is one of the fundamental distinctions between civilization and savagery. He was thinking not only of how music and the arts have extended the range of possible auditory and visual experience far beyond anything provided by the natural world, but also of the wealth of gustatory and olfactory sensations offered to civilized man. When one considers our elaborate structure of learned taste preferences it is perhaps no more surprising that we should develop a taste for tobacco than that we should have learned to like the many foods and drinks which sophisticated man consumes for taste rather than for nutritional value. Nor is the taste for tobacco unique in terms of the strength with which it is desired. Several other substances (salt, refined sugar, chocolate) are not merely enjoyed when they happen to be available, but are actively sought for, sometimes at considerable inconvenience. Brill cites as an example the case of certain South American tribes which could be induced to remain in missionary compounds because the desire which they had developed for salt could not be satisfied if they returned to the jungle. Brill further suggests that the sense of taste, like other senses, craves not only variety but also 'continuous gratification'; hence, for example, the Roman vomitoria, which were devised so that eating could be divorced

Table I. Aspects of the smoking act and possible sources of reward

Social	*Sensorimotor*	*Pharmacological*
Symbolic Communal	Oral and manual manipulation Taste and aroma Appearance of smoke	Intake of smoke constituents, especially nicotine

not only from its natural cause—the feeling of hunger—but also from its natural consequence of filling the belly. Smoking is a means of taking a substance which excites sensory organs in the lips, mouth and throat and which provides sensations of touch, taste, heat and irritation. Unlike food and drink, however, smoke does not accumulate in the body to produce satiation and discomfort and is thus an ideal medium of continuous sensory 'gratification'.

An account of the non-pharmacological sources of reward involved in smoking would not be complete without reference to the psychoanalytic interpretation of the habit. In the context of his general theory of sexuality, Freud (1905) argued that smoking and drinking (together with thumb-sucking in childhood) were primitive 'autoerotic' activities found especially in individuals in whom there was a 'constitutional intensification of the erotogenic significance of the labial region'. Bergler (1946) wrote of the childhood antecedents of smoking, 'getting something orally is the first great libidinous experience of life: breast, milk bottle, pacifier, food. The smoker reassures himself by getting something into his mouth too.'

The explanation of moderate smoking in terms of 'orality' is intuitively plausible. W. H. Auden, for example, explained his heavy smoking as 'insufficient weaning—I must have something to suck'. In the psychoanalytic literature, it is rare to find hypotheses which are general and unambiguous enough to be tested. Freudian ideas on the childhood origins of smoking, however, have been measured against scientifically valid yardsticks. There is evidence that age at weaning, although unrelated to whether or not people are smokers (and unrelated to amount smoked), is associated with the ability to give up the habit (McArthur et al. 1958). Thus, light smokers who were able to stop smoking were found to have spent an average of eight months at their mothers' breast and heavy smokers able to stop 6.8 months, whilst smokers who had never tried to give up were weaned at an average age of five months and those who had tried and failed at 4.7 months. A further association with childhood experience was found by Zucker and Van Horn (1972) who related smoking and drinking in late adolescent males to birth order and birth interval. An interaction was found between the two variables such that first-borns who had been closely followed by a second child showed a significantly greater frequency of smoking and problem drinking. This might be related to the fact that such children received less maternal attention during feeding (a narrow interpretation of 'oral frustration'). Oral frustration, although correlated with subsequent smoking, is not thereby proven to be causally related to it. It is quite conceivable that weaning practices and adult smoking are both reflections of much wider differences in child-rearing and indeed in family circumstances as a whole. Evidence that smoking is a part of a wider adult 'oral personality' is slight. Howe and Summerfield (1979) considered whether smokers and non-smokers differed in orality, as measured by such behaviours as sucking pencils, sweets or one's thumb, food-chewing and nail-biting. The smokers and non-smokers in their group of 97 student subjects did *not* differ in any of these respects. There was some evidence of greater orality amongst smokers who had never succeeded in giving up for any length of time, compared with subjects whose pattern of smoking was more intermittent; but even here, although pencil-sucking and nail-biting discriminated between the two groups, thumb-sucking and sweet-eating still did not.

The idea that smoking is associated with alcohol and coffee drinking (both basically non-nutritive oral behaviours) is more firmly based (Matarazzo & Saslow 1960). However, the fact that use of tobacco, coffee and alcohol tend to occur together can readily be explained without reference to the concept of orality. All three substances are to a large extent consumed in the kind of social context which might be more attractive to a particular kind of person. There is also the possibility that nicotine, caffeine and alcohol—all mood-altering substances—may be of greater usefulness to those with difficulties in the self regulation of affect, irrespective of any early childhood experience or of any constitutionally intensified 'erotogenic significance of the labial region'.

THE ROLE OF NICOTINE

Social factors are clearly implicated in the initiation of smoking and are likely to be of continuing relevance to the developing habit. There is also evidence for the involvement of sensorimotor rewards. However, there are three major reasons for thinking that established cigarette smokers smoke primarily for nicotine. Firstly, measuring levels of nicotine in blood and urine shows that smokers habitually absorb quantities of nicotine large enough to have profound pharmacological effects (Armitage et al. 1975). Secondly, the great majority of smokers, apparently out of choice, smoke cigarettes which yield significant amounts of nicotine and avoid cigarettes which do not. Thus 80% of the cigarettes sold in the UK in 1977 had nicotine deliveries of 1.2 mg or more (Capell 1978). This was the case despite the availability of 'mild' cigarettes which deliver as little as 0.3 mg nicotine and despite the fact that smokers had been encouraged for five years to switch for health reasons to low-tar, low-nicotine brands. Thirdly, the prevalence of smoke inhalation suggests that intake of nicotine is the *underlying purpose* (and not the unintentional by-product) of cigarette smoking. Whereas only 18% of pipe smokers and 35% of cigar smokers report inhaling moderately or deeply, the corresponding figure for (male) cigarette smokers is 77% (Lee 1976, Table 34). Unlike alkaline cigar and pipe smoke from which nicotine can be absorbed through the buccal mucosa (Armitage et al. 1978) the acidic smoke produced by a cigarette will 'deliver' its nicotine only if the smoke is drawn into the lungs. It could therefore be argued that the nature of the cigarette is such as to *necessitate* inhalation (Russell 1976), for the enjoyment of tobacco through smell and taste and the oral and manipulative satisfactions of smoking can be obtained without drawing smoke into the lungs. Inhaling smoke is not a natural behaviour and is learned at the cost of some initial discomfort. It is, however, an exceptionally fast and efficient way of administering a drug to the brain and in this respect resembles intravenous injection.

SMOKING AS NICOTINE ADDICTION

Certain forms of habitual behaviour can be conceived of as 'compulsive drug-seeking', the idea being that the body becomes so used to the presence of a particular drug that it is no longer able to function adequately in its absence. Continued use of the drug then becomes necessary simply in order to avoid the unpleasant consequences of withdrawal. The intravenous administration of opiates—the 'classical' drugs of addiction—would fall into this category and the apparent importance of nicotine in the cigarette habit suggests that continued smoking might be attributable to an analogous process. The view that smoking is essentially nicotine self-administration is widely held (Russell 1971), but extensive experimental investigation has not produced conclusive evidence that this explanation of the habit is correct.

In animals, experiments involving the administration of nicotine following the performance of a learned behaviour have shown that the drug has some intrinsic reward value and rhesus monkeys have been induced to self-administer nicotine, either by injection or by puffing on a lighted cigarette. It has, however, been difficult to demonstrate the type of dependence on nicotine which other drugs of addiction may produce in animals (Jaffe 1978).

Studies of withdrawal of smoking

In man, support for the addiction model (as outlined in Fig. 2) is provided by development of withdrawal effects in many smokers who give up the habit and the role these effects play in encouraging a return to smoking. Most descriptions of smoking withdrawal lay emphasis on heightened irritability, inability to concentrate, craving, tremors, palpitations and depression (e.g. Finnegan et al. 1945; Knapp et al. 1963). There is some evidence that chewing gum containing nicotine can be a helpful aid in cigarette withdrawal (Schneider et al. 1977) and that smokers who have successfully given up cigarettes may in turn become dependent on nicotine gum (Russell et al. 1976). There were two surprising findings, however, in a study of the time course of withdrawal effects (Shiffman & Jarvik 1976). Firstly, there was no difference in the severity of withdrawal between light and heavy smokers and, secondly, withdrawal effects were felt more severely by those who reduced but did not completely stop smoking than by those who abstained totally. Neither result would have been expected if withdrawal

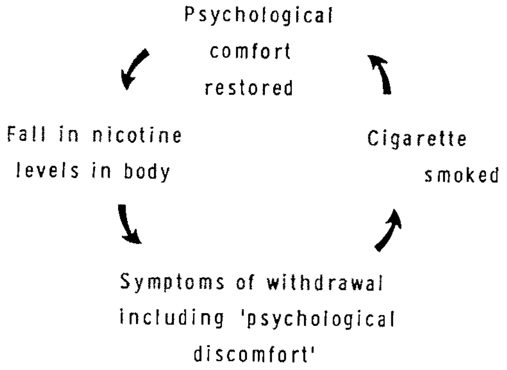
Psychological comfort restored
Cigarette smoked
Symptoms of withdrawal including 'psychological discomfort'
Fall in nicotine levels in body

Fig. 2. The addiction model

effects were due solely to nicotine deprivation. There are other reasons for questioning the view that stopping smoking is equivalent to withdrawal of the conventional drugs of addiction. The kind of withdrawal effects reported on stopping smoking are relatively mild and are of a kind which might be expected to follow the loss of psychological rewards from any 'loved' object to which a person was long accustomed and which had perhaps come to form a central part of his self-image and his support in facing the world. Secondly, there are intriguing cases of heavy smokers who give up the habit suddenly and without experiencing withdrawal. Finally, many smokers are able to refrain from smoking for relatively long periods for practical or religious reasons, apparently without experiencing hardship. Coal miners who cannot smoke at the pit face and orthodox Jews who do not smoke on the Sabbath are examples. It is unclear how the experience of these groups of people could be incorporated into a conventional addiction view of smoking (Schachter et al. 1977).

Effects of providing an alternative source of nicotine

Much human experimental research on the addiction model has been based on the attempt to show that compensatory adaptation of smoking behaviour occurs if nicotine can be provided from sources other than smoking or if the ease with which nicotine is obtained from smoking is manipulated. Any such self-regulation would suggest not only that smoking is essentially self-administration of nicotine, but that it is self-administration of a particular, preferred dose. However, practical difficulties have arisen in finding a method of nicotine administration equivalent to smoking (and no method tried so far has consistently reduced levels of smoking), whilst experiments which have varied the availability of nicotine from the cigarette have failed to dissociate the importance of nicotine from that of other smoke constituents.

Jarvik et al. (1970) found that oral administration of 50 mg nicotine tartrate daily reduced the cigarette consumption of 17 heavy smokers by only 3%. However, absorption of nicotine from the gut is very slow (Armitage 1973) and nicotine absorbed in this way, unlike that absorbed from the lungs, does not escape initial metabolism in the liver. It might therefore be expected that orally administered nicotine would be an inadequate substitute for that derived from smoking. Absorption of nicotine through the buccal mucosa is more efficient, especially when in solution at an alkaline pH, but attempts to reduce smoking through the use of nicotine chewing gum have produced equivocal results. Turner et al. (1977) found no effect on smoking and, in a study which did show some overall effect (Russell et al. 1977), the ability of the gum to replace smoking was unrelated to its capacity to provide nicotine. Thus those subjects whose plasma nicotine level with the gum was similar to that obtained from smoking were not those who least missed cigarettes. Mean blood levels of nicotine may, however, be less important than peaks: Armitage et al. (1969) found that the output of acetylcholine from the cat parietal cortex (and the extent of electrocortical desynchronization) following the multiple injection of nicotine every 30 seconds was very different from that produced by a continuous infusion of the same total dose over a 20-minute period. If the smoker is deriving his smoking 'satisfaction' from 'spikes' of nicotine-laden blood produced by each cigarette, or by each inhalation, the overall blood levels produced by nicotine gum, even if equivalent to those produced by smoking, would not necessarily substitute for the effect of cigarettes.

Intravenous nicotine injection is the method which most closely resembles smoke inhalation in terms of the speed and efficiency with which the drug is administered. However, the most recent and sophisticated attempt to substitute intravenous nicotine for that derived from cigarettes (Kumar et al. 1977) failed to produce a reduction in smoking. Subjects were given either doses of inhaled tobacco smoke (at three levels of nicotine delivery) or intravenous injections of nicotine bitartrate at two concentrations. There followed a period of ad libitum smoking during which puffing behaviour was recorded. Whereas the inhaled smoke reduced subsequent smoking (measured by total smoke volume taken and latency to first puff) in a dose-related way, no such effect was observed with the injected nicotine, even though the doses administered were within the range obtained from smoking and despite the fact that the nicotine was administered in pulses to mimic the effects of inhalation. Subjects were aware that intravenous nicotine would be administered but did not know the order in which the control and the two nicotine doses were given. Although no dose–response relationship was apparent, the pattern of smoking during intravenous administration was different from that found when nicotine was administered in smoke, the puffs taken being of smaller volume but of greater frequency. Low-volume, rapid puffing is suggestive of nervousness and it is possible that subjects' knowledge that nicotine was being given intravenously led to such an altered pattern of smoking that any dose–response effect was swamped. Another factor may have been the discomfort caused by the administration of unbuffered nicotine. For these reasons, therefore, the finding of Kumar et al., although evidence against the addiction view, cannot be taken as proof that nicotine from smoking cannot be replaced by nicotine from an alternative source.

Effects of altering nicotine delivery

The design of cigarettes can be altered so that the availability of nicotine is systematically varied. By using tobacco of different nicotine content, by varying the nicotine retention efficiency of the cigarette filter and by altering the degree of ventilation and the porosity of the cigarette paper cigarettes of different 'standard' nicotine (and tar) deliveries may be produced. The 'standard' delivery is that obtained when a cigarette is machine-smoked to a specified number of puffs, each puff being of a standard duration and volume. Human smokers, of course, do not smoke in the same unvarying way. The figures for standard delivery (which appear, for example, in the U.K. Health Department's tar and nicotine 'league tables' for commercially available brands) are therefore not an indication of the yield which will be obtained by any particular smoker on any one occasion. Nevertheless, a standard specification enables the tar and nicotine delivery of different cigarettes to be compared and gives an accurate indication of their yields relative to one another.

To obtain the same amount of nicotine from a low-yielding brand, the smoker who is used to a higher-yielding cigarette must take a greater volume of smoke, inhale more deeply, smoke more frequently and so on. Switching between cigarettes of different standard nicotine delivery therefore offers a way of investigating smoking motivation. If smokers adjust their smoking behaviour to compensate for reduced nicotine delivery, it suggests that they are smoking to obtain a particular level of nicotine intake. Reasonably consistent evidence is furnished by the 20 to 30 brand-switching experiments which have adopted this approach. Smokers who are used to cigarettes of medium delivery increase the number of cigarettes smoked when switched to a lower-yielding brand (Stepney 1980). The increase in cigarette consumption is, however, relatively small, a 50% reduction in yield producing a rise in consumption of about 10%. The major compensation appears in the pattern with which individual cigarettes are smoked: the number of puffs taken is greater, puffs are of longer average duration and of greater volume, the cigarette is smoked to a shorter butt length and the smoke is inhaled more deeply. The extent to which these changes in smoking behaviour compensate for differences in standard delivery can be estimated by measuring the intake of smoke constituents. Ashton et al. (1979*b*) describe 12 habitual smokers who were studied whilst smoking their usual medium-delivery cigarettes (yielding 1.4 mg nicotine and 18 mg tar) and whilst smoking two experimental brands, one with a higher delivery (1.8 mg nicotine, 27 mg tar) and the other with a lower yield (0.6 mg nicotine, 7 mg tar). Measurement of actual nicotine intake (based on blood plasma and urine nicotine concentrations) showed very much smaller differences between brands than would have been expected on the basis of the differences in standard delivery. By 'over-smoking' the low-yielding cigarettes and 'under-smoking' the high-yielding brand the subjects had in fact compensated for two-thirds of the differences in machine-smoked delivery between brands. The changes in smoking behaviour which follow brand-switching are therefore entirely consistent with the view that smokers seek to maintain their habitual levels of nicotine intake when smoking cigarettes of different nicotine delivery. The major problem with this line of reasoning, however, is that cigarettes which differ in nicotine delivery also differ in many other ways. For example, in the experiment cited, nicotine yield varied with that of tar. Although, as far as is known, the tar phase of cigarette smoke contains no substances which are 'psychologically active', the tars presumably contribute to taste and aroma and to the particular sensations accompanying smoking (such as the 'scratch' experienced at the back of the throat on inhalation). Thus smokers seeking merely to maintain the intensity of the pleasurable sensations involved in smoking (rather than the nicotine intake) would respond to changes in brand strength in exactly the way observed. The importance of nicotine, relative to that of other smoke constituents, cannot therefore be conclusively established on the basis of such experiments.

SMOKING AS A PSYCHOLOGICAL TOOL

Support for the crucial role of nicotine, however, is provided by an alternative approach to smoking, which considers that cigarettes may be used as a 'psychological tool'. This view differs from the addiction model in suggesting that smoking continues to be rewarding, not simply as a way of avoiding nicotine withdrawal, but as a means of controlling arousal. The concept of smoking as a psychological tool is supported by experiments which show that cigarettes, under certain circumstances, have a stimulant effect, increasing a subject's ability to attend and maintaining high levels of performance on monotonous or fatiguing tasks. There is also evidence which suggests that smoking can act as a depressant or sedative in reducing the disruptive effects of stress on behaviour.

In order to account for these varied findings it is necessary to argue that smoking is capable of having either arousal-increasing or arousal-reducing properties (Fig. 3). Smokers themselves have claimed that cigarettes can have these apparently contradictory actions, as have certain commentators on smoking since James I who (in 1604) wrote of tobacco 'being taken when they go to bed it makes one sleep soundly, and yet being taken when a man is sleepy and drowsy, it will, as they say, awake his brain, and quicken his understanding'. Recent work, concerned primarily with EEG analyses of the effect of nicotine on arousal, has shown that what is claimed for smoking may be more substantial than a mere 'pipe-dream' of the smoker.

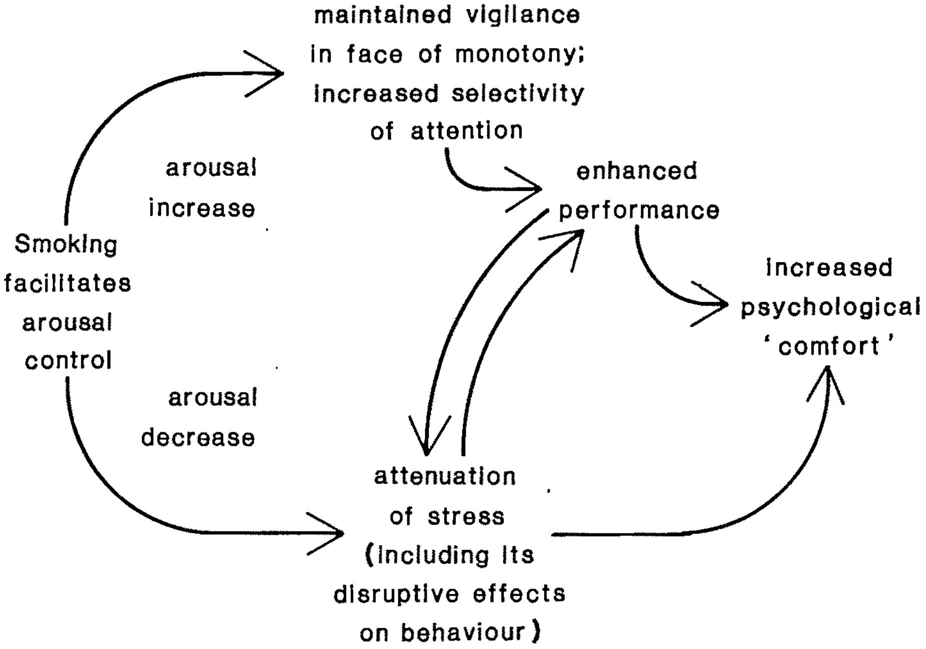
maintained vigilance in face of monotony; increased selectivity of attention
arousal increase
enhanced performance
Smoking facilitates arousal control
increased psychological 'comfort'
arousal decrease
attenuation of stress (including its disruptive effects on behaviour)

Fig. 3. Smoking as a 'psychological tool'

The control of arousal

Arousal can be thought of as a dimension with sleep at one end and hyperactivity at the other, and drowsiness, boredom, alert interest, etc. as stages in between (Claridge 1970). This concept of arousal, however, involves difficulties since it relates both to overt behaviour and to how an individual 'feels' and it is clear that one can feel alert, for example, and yet be physically totally inactive. The concept of arousal has therefore been extended to incorporate physiological activity and two sets of measures have been found useful in this respect. Variables such as heart rate, blood pressure and sweating (reflected in changes in skin resistance to the passage of a weak electric current) have been used as measures of autonomic nervous system activity whilst various aspects of the electroencephalogram have been developed as an index of CNS activity. Under 'normal' conditions EEG activity varies systematically with changes in arousal assessed by other intuitively plausible criteria. Thus in a drowsy human subject, the EEG is typified by low-frequency, high-amplitude (alpha) waves, whilst a high-frequency low-amplitude pattern of EEG activity characterizes states of alert concentration. The EEG has therefore been extensively used as an objective measure of the effect of drugs on arousal: stimulant drugs (such as amphetamines) shift the pattern of EEG activity in the direction associated with alertness and depressant drugs (such as barbiturates) have the opposite effect.

In animals nicotine has generally been found to have a stimulant effect, manifested in the desynchronization of the electrocorticogram. Domino (1967) showed that this effect was due to the direct action of nicotine by demonstrating that adrenaline and 5HT, which are released by nicotine, do not themselves have the same desynchronizing effect. Much of the work on the action of nicotine in animals has been performed using doses within the range obtained by smoking, and Phillis and York (1968) have shown that nicotine and tobacco smoke are equivalent in their effects on cortical neurone firing in the cat.

In man, a number of experiments (e.g. Knott & Venables 1977) make it clear that the effect of smoking, as measured by various forms of frequency analysis of the EEG, is one of activation. Using a different EEG measure, the frequency with which the photic driving response could be elicited, Vogel et al. (1977) also judged the effect of smoking to be stimulant and suggested that smokers suffered from a central adrenergic insufficiency which could be countered by smoking. However, Mangan and Golding (1978) demonstrated that the effect of smoking on the human EEG depends on the circumstances in which a cigarette is smoked. Smoking was found to have a depressant effect on the EEG (increasing the proportion of alpha activity) when subjects were stressed by being exposed to intermittent bursts of 106 dB white noise, but a stimulant effect (decreasing the proportion of alpha activity) under conditions of low arousal induced by mild sensory isolation. This finding supported that of Ashton et al. (1974, 1979*a*) who had earlier found an interaction between nicotine effect, personality and total dose, when studying the contingent negative variation (CNV): a slow potential shift in the EEG occurred in the few seconds between an alerting stimulus and a stimulus to which the subject must respond. The CNV was consistently decreased in some subjects (depressant effect) and consistently increased in others (stimulant effect). The effects of smoking could be replicated by intravenous injection of 'smoking-doses' of nicotine and a dose–response relationship was established in which smaller doses of nicotine had a stimulant effect on the EEG and larger doses a depressant one. More extraverted smokers were found to have a somewhat slower rate of nicotine intake from smoking than introverts, supporting Eysenck's view of the extravert as 'stimulation hungry' and the introvert as 'stimulation shy' (Eysenck 1973).

Smoking and stress

Frith (1971) conducted a systematic questionnaire investigation into the desire people would have to smoke under different imagined circumstances and found that smokers felt they needed cigarettes both under low-arousal conditions (for example waiting for a train or having a quiet evening with friends) and when stressed (by, for example, an important job interview or a horrifying film). Observational evidence of people's smoking habits under such conditions, however, is surprisingly sparse. Ben-Meir (1977) records that the percentage of smokers and number of cigarettes smoked in Israel rose considerably during the Yom Kippur War. An unpublished report to the Tobacco Research Council by National Opinion Polls showed that smoking tended to be more intensive under conditions of excitement (though no quantitative account of the results was presented) and a number of surveys (e.g. Thomas 1973) have found that smoking is associated with stressful life events and high levels of personal anger and anxiety. There is thus evidence that smoking and stress are in some way related. However, evidence that smoking may be of value in *reducing* the effects of stress derives primarily from the use of nicotine in animal studies. Nicotine has been shown to suppress aggressive behaviour in the cat and to reduce the frequency of biting attacks in monkeys given electric shocks (Hutchinson & Emley 1973). In both studies the reduction in aggressive behaviour was selective in that other behaviours were unchanged. Hutchinson and Emley equate the monkey biting-attack with jaw-clenching in man and find a direct parallel with the results of their animal experiments in the finding that 5 mg of nicotine administered in drinking water to human subjects decreased the frequency and force of jaw contractions to 110 dB tones. They had previously established that smokers who were in withdrawal showed an increased frequency and force of spontaneous jaw contractions; the effects of nicotine in drinking water, however, applied also to non-smokers and therefore seemed to be a genuine effect of the drug.

In a further experiment, Hutchinson and Emley trained monkeys and rats to press levers for food. During the training period, occasional tone stimuli were presented together with an electric shock. In the post-training period, presentation of the tone alone, which had become a conditioned stressor, disrupted food-acquisition behaviour. Nicotine in doses of 40–400 μg/kg countered this stress-induced suppression of behaviour. An analogous effect was demonstrated by Nelsen (1978). The spontaneous activity of rats, which is normally replaced by freezing in the presence of a cat, was significantly less affected in animals given repeated subcutaneous nicotine doses of 100 μg/kg. The reduction in freezing response was more marked in a highly emotional group than in rats with low emotionality. Nicotine administration also reduced the disruption of behaviour normally caused by stimulation of electrodes implanted in the reticular formation. This, together with the fact that nicotine affects electrical activity in the cortex and hippocampus, but not in the reticular formation, has led Nelsen to suggest that the effect of nicotine and of smoking is to alter the relative level of activity in the two arousal systems hypothesized by Routtenberg (1968). On this theory, the effectiveness of smoking in reducing stress and in maintaining performance is mediated by an increase in the goal-directed arousal of limbic structures whilst the generalized arousal mechanism of the reticular formation is reciprocally inhibited.

Hall and Morrison (1973) showed that rats trained to avoid electric shocks by pressing a lever performed more successfully with nicotine and could become dependent on the drug to maintain high levels of performance. When, however, the task was made 'easier' by providing a feedback signal following the lever-press, rats in withdrawal from nicotine did not show impaired performance. It is inferred (on the basis, for example, of the increased frequency of gastric ulcers in animals on avoidance tasks without feedback) that a signal following lever presses reduced the stressfulness of the task and so decreased the need for nicotine.

It is fairly clear therefore that nicotine can play a part in reducing the effects of stress on behaviour in animals. There is less evidence of this effect in man, although the results of two studies suggest that this might also be the case. Dunn (1978) reports that subjects who smoked did not show impaired performance on a task when they were systematically cheated of points which they could later convert to money. Interestingly, the increases in self-rated aggression were not different in the smoking, smoking-deprived and non-smoker groups, although the disruptive effect of the aggression was less in those who were smoking. (In contrast, Heimstra et al. (1967) had previously reported that smokers did not increase their ratings of aggression over a six-hour period of simulated driving, whilst both deprived smokers and non-smokers did.) Evidence that cigarettes might be used to combat the disruptive effects of stress on performance comes also from another source. Myrsten et al. (1975) studied eight subjects who reported smoking in situations of high arousal and eight who were typically 'low-arousal smokers'. Both groups performed a task of two levels of complexity when smoking and when not smoking. The low-arousal smokers performed better when smoking only when the task was relatively simple and the high-arousal smokers only when the task was complex. When they were not smoking, the high- and low-arousal subjects performed equally well on both tasks. The pattern of results suggested that those subjects who normally smoked in situations of high-arousal were using the arousal-reducing effect of cigarettes to improve their performance when stressed by the greater demands of the complex task.

The effect of smoking on performance

The evidence reviewed suggests that the arousal-decreasing properties of nicotine (and smoking) may reduce the disruption of behaviour by stress. There is also evidence which suggests that nicotine and smoking may enhance performance by increasing arousal. This is especially so on monotonous tasks requiring sustained vigilance. Mangan and Golding (1978) reported that smoking a single cigarette before an auditory vigilance task improved the performance of cigarette smokers by decreasing the number of occasions on which the signal was wrongly thought to be present. Frankenhauser et al. (1971) compared the performance of a group of smokers with and without cigarettes on a monotonous reaction-time task lasting 80 minutes. Smoking cigarettes at 20-minute intervals through the experiment prevented the gradual slowing in the speed of reaction which occurred when no cigarettes were smoked. These two studies can be criticised on the grounds that the comparison made (between smokers smoking and smokers not smoking) confounds possible beneficial effects of smoking with possible impairment of performance due to cigarette withdrawal. It is uncertain whether a period of one to two hours is sufficient to produce abstinence effects in the kind of habitual (but moderate) smoker participating in such research, but the possibility cannot be excluded. Two further studies, which have involved a comparison between smokers while smoking and non-smokers, are therefore of great importance. Wesnes and Warburton (1978) found that smokers who were smoking did not show the decrement in performance (on an 80-minute vigilance task) which occurred in both smoking-deprived and non-smoking groups. A similar result was obtained by Tarriere and Hartemann (1964) in a study involving a combined surveillance and guiding task intended to simulate driving.

The association between smoking and alcohol consumption has been well documented in both normal and clinical populations (e.g. Griffiths et al. 1976). Myrsten and Andersson (1975) found that smoking can counteract the slowing of reaction time produced by alcohol, whilst actually increasing subjective intoxication, and the possibility that the stimulant properties of nicotine might help to counter the depressant effects of alcohol offers an intriguing explanation of their frequently observed combined consumption.

The effects of smoking on learning and memory in man, like the apparent usefulness of cigarettes in maintaining vigilance and attention, can be explained by the arousal-increasing properties of nicotine. Smoking has little (and possibly even a detrimental) effect on the acquisition of material, but seems to improve retention and later recall. High arousal is disruptive of initial learning, but facilitates the consolidation of the memory trace and therefore enhances ultimate memory. Work involving nicotine administration in mice supports this view of the effects of smoking on memory (Flood et al. 1978). The injection of nicotine (or of caffeine or amphetamine) was found to block anisomycin-induced amnesia following training on an avoidance task. A greater intensity of electric shock, a more arousing stimulus, had an effect similar to that of these stimulant drugs in decreasing amnesia.

Two Views of Smoking Motivation

The addiction approach views the motivation for smoking as the need to prevent the aversive effects of nicotine withdrawal. The psychological tool view differs in believing that smoking is rewarding, not simply as a means of preventing the consequences of nicotine deprivation, but in its own right as a means both of reducing the disruptive consequences of stress and of enhancing performance. The arousal control view, however, does not preclude considering smoking as a 'dependence disorder'. It is entirely possible that smokers could become reliant on cigarettes as a convenient method of mood manipulation. The very regularity with which smokers consume cigarettes, however, poses problems for the psychological tool view. A group of 40 medium- and low-tar smokers of 5–50 cigarettes per day was asked to record the number of cigarettes smoked each day for a week and each hour for two days, one a working day, the other a rest day. The average consumption of the group as a whole, and the pattern of smoking of each individual, showed remarkable consistency (Stepney, unpublished data). Smokers spaced their cigarettes regularly through the day, light smokers smoking a cigarette every one or two hours and heavy smokers up to three or four per hour. The impressive regularity with which even light smokers consume cigarettes needs to be taken into account in any explanation of the tobacco habit. Although this regular pattern of smoking suggests the kind of 'topping up' of nicotine levels envisaged in the addiction view of the habit, it is possible to explain this kind of behaviour in terms of learning theory. Evidence from 'diaries' kept by smokers indicates that only occasional cigarettes (those smoked under stressful conditions or during concentrated work, for example) are perceived as being particularly rewarding (Mausner & Platt 1971). In terms of learning theory, it would be sufficient for the use of a cigarette to be rewarding in this way on certain occasions only, for the behaviour to be powerfully reinforced and therefore often repeated.

Implications

The evidence available about smoking motivation presents a picture which is somewhat contradictory and certainly incomplete. Nevertheless, where smoking has been shown to affect mood and performance in man, the results of experiments correspond to what smokers themselves say about the reasons for, and effects of, smoking. The apparent usefulness of smoking as a psychological tool must therefore be taken into account in any comprehensive evaluation, for if smoking does confer psychological benefits, the question of how to stop people smoking will not be answered while this is ignored.

The view of smoking as a psychological tool does not justify the cigarette habit, for it is extremely unlikely that any psychological benefits would outweigh the health risks involved. If, however, it were established that smoking had psychological effects which could reasonably be regarded as advantageous, three changes in emphasis might follow. Firstly, the smoker might be seen not so much as an irrational addict but as someone weighing genuine benefits (however small and short-lived) against the likelihood of serious long-term penalties. Secondly, the question of why some people find it 'necessary' to smoke and others do not would come to the fore. It has been established that smokers and non-smokers differ to a small but statistically significant extent in certain aspects of personality. Eysenck et al. (1960) showed that the number of cigarettes smoked was positively associated with extraversion, and Cherry and Kiernan (1976) have demonstrated that the likelihood that an individual will become a smoker between the ages of 16 and 25 is related to both neuroticism and extraversion at the age of 16. This suggests that smokers may be constitutionally less well-equipped to control their level of arousal. Although the search for constitutional differences between smokers and non-smokers has not yet revealed any convincing evidence on this point, research into the smoking behaviour of twins has shown that genetic identity increases the similarity of smoking habit (Friberg et al. 1959), indicating that some genetic (and therefore presumably constitutional) factor is involved. The question of why some smoke and others do not might be answered by examining differences in environment. If smoking can be employed to manipulate arousal one would expect the habit to be of greatest use to those whose environment is most stressful. Can the predominance of smoking in the lower socio-economic groups be explained in this way? Is it the case that those higher up the social scale have more 'coping mechanisms' (skills, money, influence) which can replace smoking?

The third change in emphasis would stem from the apparent primacy of nicotine. If people smoke for nicotine, and if nicotine is a genuinely 'useful' drug (rather than the agent of a meaningless and unfortunate addiction), it would make sense to pursue further the idea of maintaining the nicotine delivery of cigarettes whilst reducing that of tar and carbon monoxide (Russell 1974). Cigarettes of safer tar/nicotine ratios are being produced on an experimental (and recently also on a commercial) basis (Stepney 1979). The precise effects of this alteration in cigarette design on smoking behaviour are not yet clear. The attempt to provide nicotine from some source other than smoking is also worthy of further attention. Nicotine chewing gum and tablets have not met with great success, but the failure of present-day tactics does not mean that the general strategy is unreasonable. The American National Cancer Institute has recently expressed interest in the possibility of providing nicotine in the form of an aerosol spray and it is not inconceivable that the smoker's packet of cigarettes might one day be replaced by an inhaler. A recent report (Jacobson et al. 1979) suggests that nicotine vapour inhaled from a 'non-combustible cigarette' could prove a practical alternative to the conventional product. Serum nicotine levels during normal smoking and during vapour inhalation were similar, and subjects reported themselves satisfied with this new method of nicotine administration.

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Chris Drury. World Champior oarsman and asthmatic.

Chris Drury, 27, has suffered from both asthma and eczema sinc childhood.

In fact, between the ages of 7 and 10, he was regarded as being to ill even to participate in school sport

After that, he did get slightly better and at 13 was well enough to take up rowing.

At 16, he began to notice that exercise induced his asthma attacks

He was put on Intal.

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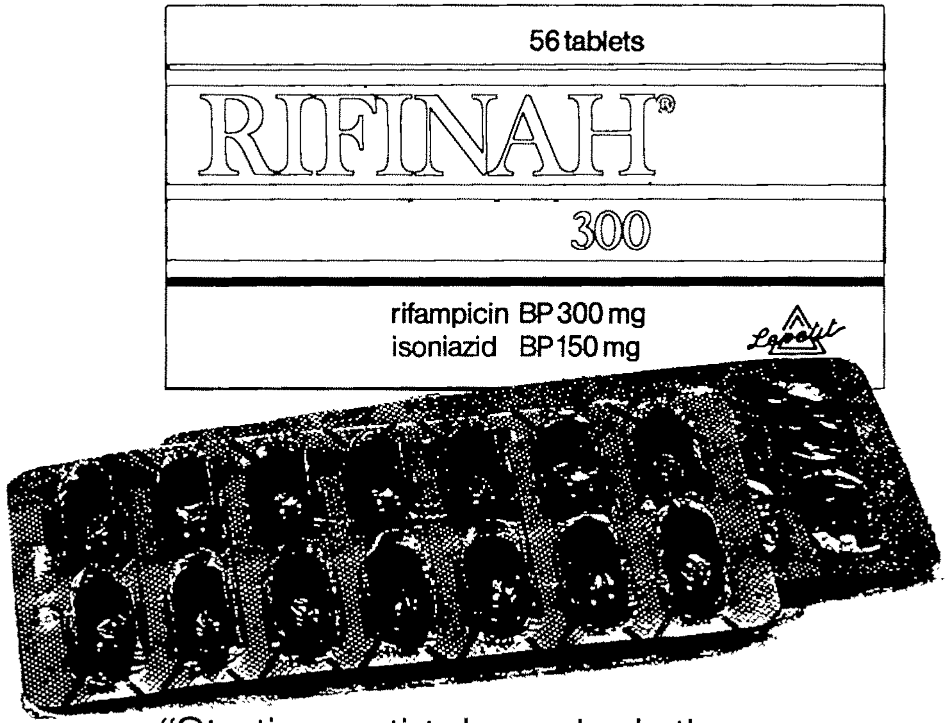

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A PATHOLOGICAL STUDY FOLLOWING BRONCHIAL ARTERY EMBOLIZATION FOR HAEMOPTYSIS IN CYSTIC FIBROSIS

A. J. FAIRFAX, J. BALL, J. C. BATTEN AND B. E. HEARD

Departments of Medicine and Pathology, Brompton Hospital, London

Summary

A detailed post-mortem study is reported of an adult with cystic fibrosis who died in respiratory failure three weeks after selective bronchial artery embolization with gelatin sponge to treat severe haemoptysis. Bronchial arteriography during the procedure showed complete occlusion of the vessel supplying the right upper lobe and following this the bleeding stopped. However, post-mortem angiography of the same vessel demonstrated disappearance of much of the injected material with contrast bypassing the remaining gelatin to fill the peripheral bronchial arterial bed. This report therefore adds pathological evidence to previous clinical reports which have suggested that this procedure may not produce permanent occlusion of the embolized bronchial artery.

INTRODUCTION

Minor haemoptysis is a common symptom in adolescents and adults with cystic fibrosis. Massive haemoptysis occurs in approximately 7% of cases (di Sant'Agese & Davis 1979) and is a serious and sometimes fatal complication of the disease. The bleeding usually occurs from dilated bronchial arteries which supply the bronchopulmonary anastomoses found in peribronchial granulation tissue (Wentworth et al. 1968). In the past the results of medical therapy have been poor (Holsclaw et al. 1970). This has led to the use of a variety of active diagnostic and therapeutic measures such as the use of bronchoscopy and of bronchial arteriography to localize the source of bleeding (Fellows et al. 1975) and bronchial artery embolization to stop haemoptysis (Schuster & Fellows 1977). Gelatin foam is usually selectively injected into a bronchial artery under radiological control. There have been few published reports of the pathological effects of this procedure on the human lung. In this study we describe the post-mortem arteriographic and pathological findings of a patient with cystic fibrosis who died three weeks after an apparently successful bronchial arterial embolization for severe haemoptysis.

Case Report

A 35-year-old man was admitted to the Brompton Hospital in February 1979 because of recurrent haemoptysis. Cystic fibrosis had been diagnosed at 20 months on the basis of persistent cough, loose stools with absent tryptic activity and a sweat sodium concentration of 134 mmol/litre. Previous complications had included rectal prolapse when he was aged three years and pneumonia when aged five. He had recurrent chest infections with *Haemophilus influenzae* and *Staphylococcus aureus* isolated up to 1973 and mucoid *Pseudomonas aeruginosa* persistently from that date. He was married but infertile from azoospermia. He was known to be allergic to *Aspergillus fumigatus* with a positive immediate reaction on skin testing and a dual reaction on bronchial challenge. Up to admission to hospital he was able to climb two flights of stairs without difficulty and was in full-time employment. Over the last four years, however, his respiratory function had deteriorated progressively from an $FEV_1/FVC = 1200$ ml/2500 ml (predicted = 4720 ml/5580 ml) to 750 ml/1600 ml. The PEFR had similarly decreased from 460 litres/min to 160 litres/min. The chest radiograph showed persistent mottled shadowing particularly in the right upper lobe. His treatment had included continuous oral broad-spectrum antibiotics for the last 12 years and intermittent courses of intravenous gentamicin and carbenicillin since 1973. He had had one previous haemoptysis aged 19 years.

In the preceding two months he had had two small haemoptyses and two days before admission had coughed up a cupful of fresh blood. In hospital haemoptysis of approximately 800 ml occurred and he became faint, sweaty and frightened. Prothrombin time was prolonged at 16 sec (control 12 sec) and vitamin K was given. The haemoglobin dropped from 14.7 g/dl to 12.4 g/dl and PCV from 0.43 to 0.36. He was transfused two units of blood. Fibreoptic bronchoscopy at this time showed that bleeding had stopped and failed to identify the source. Intravenous gentamicin and carbenicillin were also given. After five days, however, haemoptysis recurred, initially in small amounts, and then more than 400 ml/day. A second bronchoscopy identified the source as either the right upper or the middle lobe. Nine days after admission to hospital a right bronchial arteriogram was performed under general anaesthesia. A single tortuous, grossly hypertrophied vessel supplied the right upper lobe (Fig. 1, left) and this was successfully embolized (Fig. 1, right) with 10 ml of gelatin suspension in normal saline containing approximately 0.5 ml of gelatin sponge (Sterispon No. 2).

Postoperatively the patient suffered respiratory failure: the Pa_{O_2} fell from 11.2 kPa to 7.1 kPa on 24% oxygen, the Pa_{CO_2} increased from 6.1 kPa to 10.1 kPa. However, he had no further haemoptysis. For three days there was a pyrexia up to 38°C. The sputum altered after embolization,

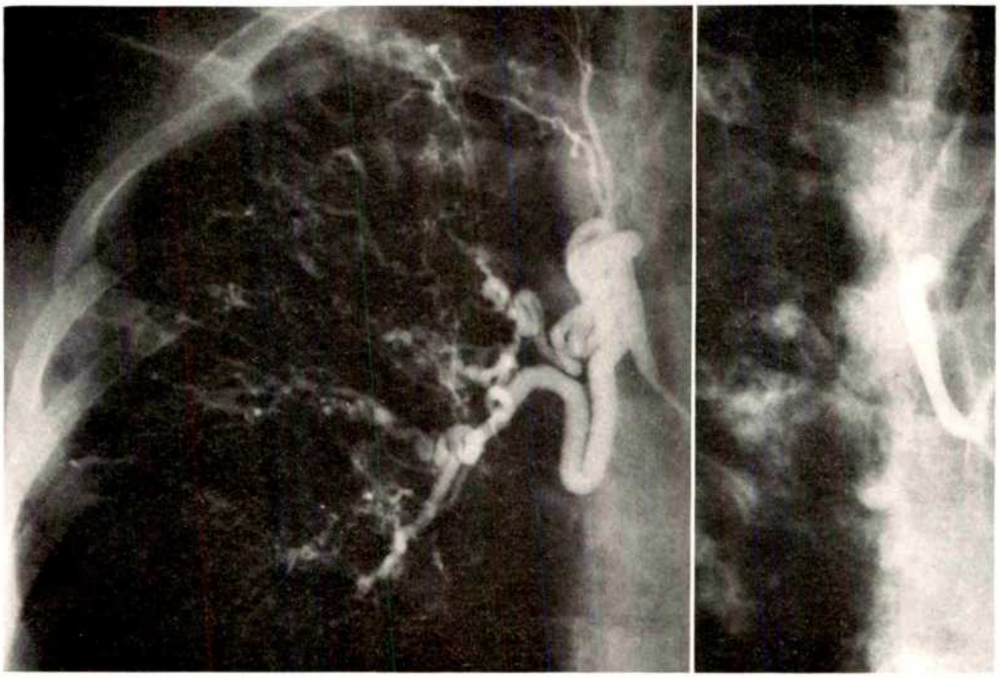

Fig. 1. Selective bronchial arteriograms. *Left*, A grossly hypertrophied vessel supplying the right upper lobe. *Right*, After embolization, showing complete occlusion of the vessel near its origin from the aorta

becoming scanty and tenacious. Five days after the procedure he complained of right pleuritic pain and was treated with physiotherapy, antibiotics and oxygen. However, his breathlessness slowly increased and he died in respiratory failure 20 days after bronchial artery embolization.

At autopsy, the heart and lungs were removed in one block and dissection was carried out to identify and mobilize the right main bronchial artery which was very dilated and tortuous. A cannula was inserted into this vessel which was patent, and a warmed suspension of barium sulphate as 80% Micropaque in gelatin was run in over a period of 30 minutes using the technique of Turner-Warwick (1963). The suspension was observed to run in freely from the start and contrast reappeared draining from the pulmonary veins. The right lung was then isolated from the thoracic block and subsequently radiographed to show the right bronchial artery and outline any residual embolic material (Fig. 2).

The lung was then distended with 10% formol saline for two weeks and cut in 8 mm thick sagittal slices. As a control, a sample of the gelatin sponge used for embolization was processed and cut in an identical manner to the lung tissue. This was compared with the embolic material found in the bronchial artery.

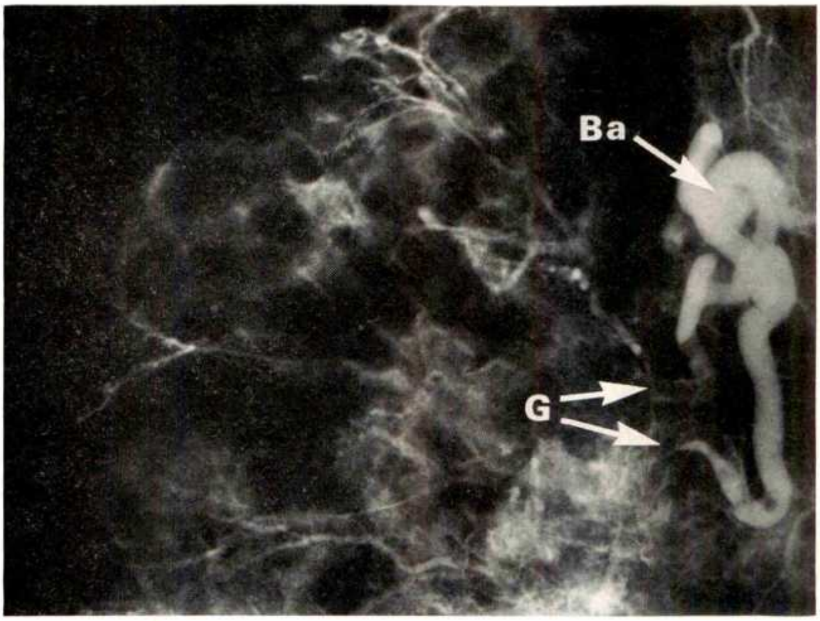

Fig. 2. Post-mortem bronchial arteriography shows that the proximal part of the artery (Ba) is now patent and sufficient contrast is bypassing the remaining embolized gelatin (G) to fill the bronchial arteriolar bed (whole unfixed right lung)

RESULTS

The initial 40 mm of the right main bronchial artery was found on dissection to be filled with contrast medium and several proximal branches also were filled. The central part of the lumen of the bronchial artery branches in the region of the hilar lymph nodes contained a soft brown substance which was surrounded by flecks of Micropaque. Several bronchi and dilated small airways showed submucosal vessels containing contrast, the most peripheral being 10 mm beneath the visceral pleura. The original bleeding point was not demonstrated.

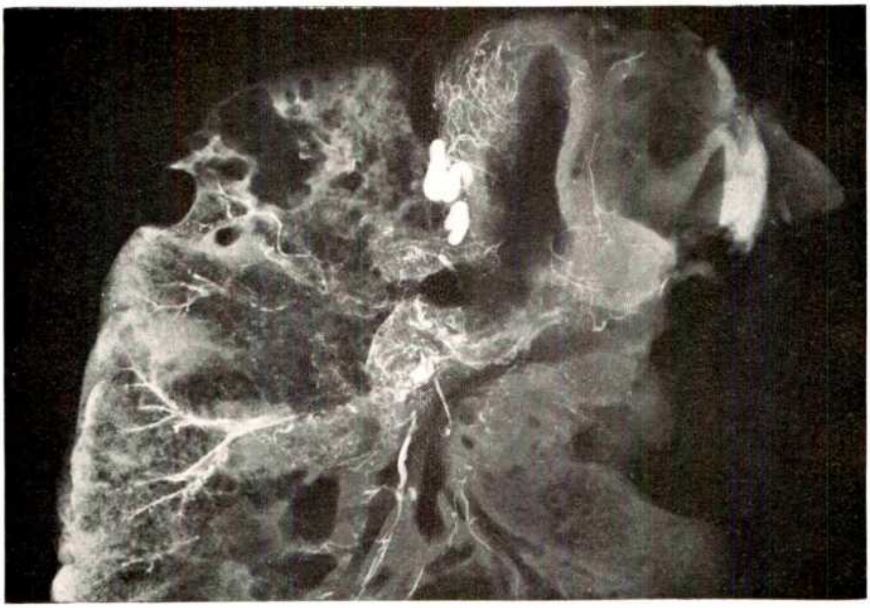

Fig. 3. Post-mortem radiograph of 8 mm lung slice showing cystic bronchiectasis in the upper lobe extending to the pleural surface

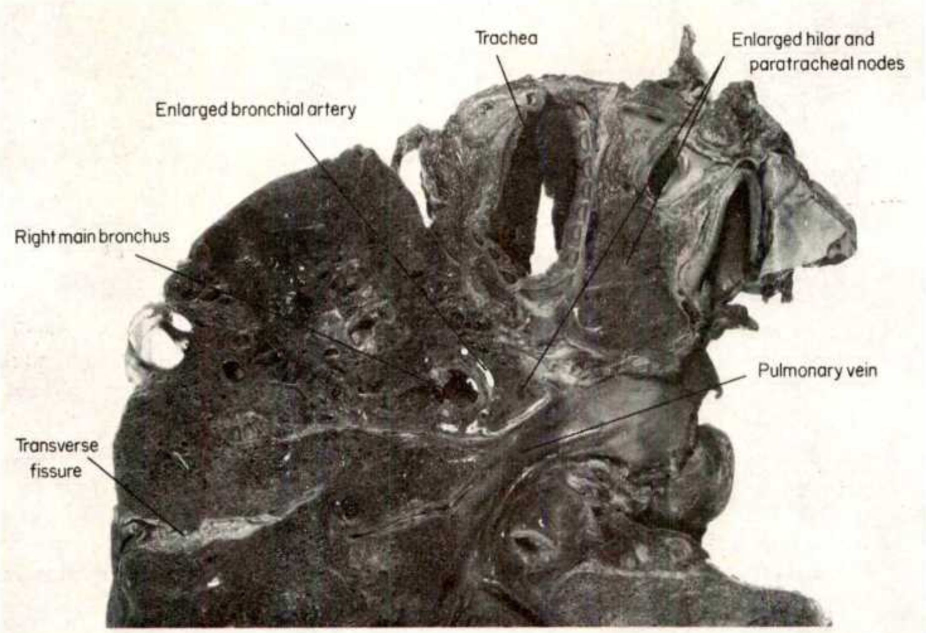
Trachea
Enlarged hilar and paratracheal nodes
Enlarged bronchial artery
Right main bronchus
Pulmonary vein
Transverse fissure

Fig. 4. Photograph of the same slice as in Fig. 3, demonstrating the enlarged bronchial artery branches in close relation to the right main bronchus

Bronchiectasis and cystic cavities associated with the long history of cystic fibrosis were seen throughout the lung but were more obvious in the upper than in the lower lobe (Figs 3 and 4). Interlobar adhesions were noted in both the transverse and oblique fissures.

In histological section, the lungs showed patches of severe fibrosis and scarring with the formation of small cysts. The bronchi and bronchioles were dilated and their walls were thickened due to marked chronic inflammation and submucosal gland hyperplasia. Scattered bronchioles contained purulent material and showed foci of epithelial ulceration. The larger branches of the right main bronchial artery were filled with gelatin sponge and there was some evidence of organization near the endothelial surface (Fig. 5). In small vessels the embolized gelatin was mixed with Micropaque and indeed occasional small branches contained Micropaque only while the parent artery contained mainly gelatin sponge (Fig. 6).

The general post-mortem examination revealed changes of cystic fibrosis in other organs. The liver showed an irregular fine fibrosis macroscopically and histologically. The pancreas was soft and showed total exocrine atrophy with fat replacement. The appendix was macroscopically normal, but showed a microscopic focus of mucosal hyperplasia. The seminal vesicles were dilated and the vas deferens was cord-like and had no lumen.

Discussion

The severe haemoptysis which occurs in cystic fibrosis is thought to result from the rupture into airways of dilated bronchial arteries serving bronchopulmonary anastomoses. The normal bronchial artery is a minute vessel but early studies in cystic fibrosis showed

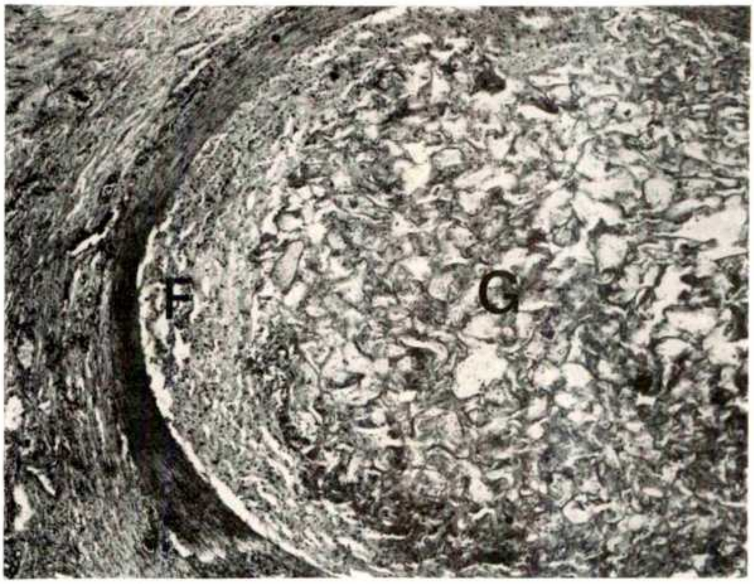

Fig. 5. Medium-sized branch of the right bronchial artery containing a central plug of embolized gelatin sponge (G) with some fibroblast proliferation (F) between it and the endothelium. Micropaque was not seen in this vessel. H + E × 37

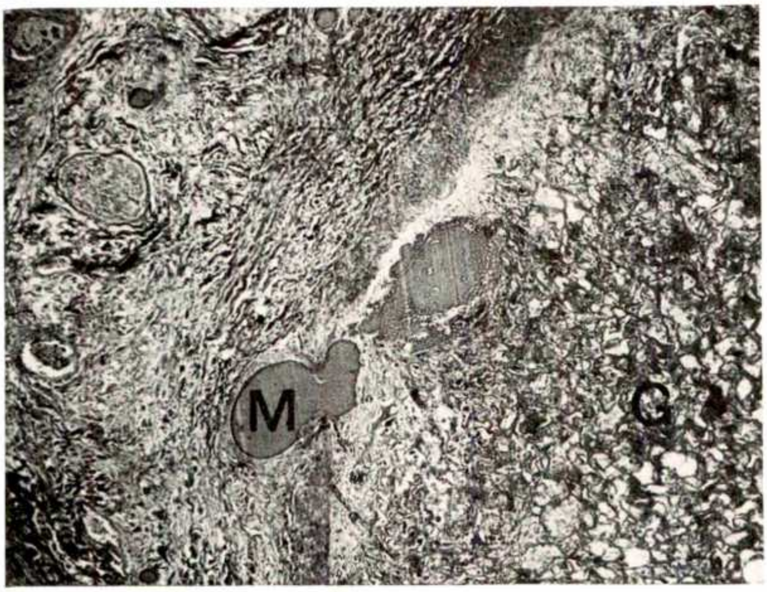

Fig. 6. A main branch of the bronchial artery containing a plug of gelatin sponge (G) but with a patent tributary containing Micropaque (M) only. Martius yellow, brilliant crystal scarlet and aniline blue × 37

that the bronchial arteries become tortuous and dilated in childhood (Mack et al. 1965) and are responsible for a detectable left-right shunt (Moss et al. 1968). These shunts develop predominantly in the florid peribronchial granulation tissue of cystic fibrosis and increase in size and number with increasing severity of the disease (Wentworth et al. 1968).

Haemoptysis in cystic fibrosis may be massive and persistent, as in this case, resulting in a threat to life. Holsclaw et al. (1970) reported that massive haemoptysis frequently heralded death in cystic fibrosis on the basis of 19 cases of whom six died during haemoptysis and a further seven who died within six months of the episode. They suggested that as a result of the unsatisfactory outcome from conservative therapy, more aggressive measures be taken. A more recent study (Stern et al. 1978) has emphasized the importance of exacerbations of pulmonary infection as a cause of haemoptysis in cystic fibrosis and these authors noted that the majority of bleeds stopped within four days with antimicrobial and supportive therapy.

The treatment of haemoptysis by interruption of the bronchial arterial supply by surgery or embolization procedures depends partly for its success on the accurate localization of the source of bleeding and this is best achieved by bronchoscopy during bleeding (Holsclaw et al. 1970) or in a few cases by selective bronchial arteriography (Fellows et al. 1975). The treatment of haemoptysis by bronchial arterial embolization using gelatin foam is a successful procedure usually performed under local anaesthesia in both neoplastic and inflammatory conditions including cystic fibrosis (Rémy et al. 1977). Schuster and Fellows (1977) reported eight patients with cystic fibrosis treated in this way for haemoptysis. All were successful in stopping bleeding but two required multiple embolizations and two died within one month of the procedure.

The post-mortem angiographic findings in this case were thought to represent a true picture of the bronchial artery immediately prior to death. The main vessel was observed to be patent for its first 40 mm on removal from the body and before the injection of Micropaque. This contrasts with the complete occlusion of the vessel near its origin from the aorta after embolization (Fig. 1, right). Also, there was initial free flow of Micropaque into the bronchial artery when injected at a physiological pressure.

The techniques and materials for therapeutic arterial embolization have been reviewed (Allison 1978). Embolization with gelatin appears to be relatively safe but the procedure is only palliative since the material is reabsorbable. Revascularization of previously embolized vessels has been described in vivo after several months and this may necessitate the repetition of the embolization at a later date (Bookstein et al. 1977; Rémy et al. 1977). The size of the gelatin fragments, which are usually cut into small pieces from a thin sheet of gelatin sponge, is said to prevent their entry into the pulmonary arteries (Rémy et al. 1977). Infarction of tissue supplied by the bronchial artery after embolization has been described (Rémy et al. 1977) but is rare.

Infarction of other tissues such as the spinal cord during embolization is a more serious hazard and neurological complications have been reported in a patient with cystic fibrosis treated by this technique (MacErlean et al. 1979).

Bronchial artery embolization is a successful palliative measure for stopping haemoptysis in cases where more conservative measures have failed (Rémy et al. 1977). Our study has shown in one case, however, that although some of the gelatin remained in situ after three weeks, much of the injected material had disappeared from the arterial lumen by this time and very little of it became organized to produce a permanent occlusion of the blood supply.

ACKNOWLEDGEMENTS

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ULTRASOUND IN THE DIAGNOSIS AND MANAGEMENT OF PLEURAL DISEASE

D. J. LIPSCOMB AND C. D. R. FLOWER
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Summary

A-mode ultrasound investigation has been performed in 62 patients, of whom 35 presented problems of diagnosis and management of pleural disease. In seven patients with known pleural effusions in whom aspiration had failed ultrasound correctly identified fluid at a site different from the aspiration attempts and in all seven cases it was successfully removed. The remaining 28 patients had the radiographic appearances of localized pleural disease and ultrasound correctly distinguished fluid and solid lesions in 26. We found ultrasound to be a simple and reliable technique which was particularly valuable in locating fluid for aspiration and in distinguishing between fluid and pleural thickening. The simplicity and 'bedside' availability of ultrasound offered certain practical advantages over radiography.

INTRODUCTION

Although pleural disease is common it continues to pose problems of diagnosis and management. Correct interpretation of the chest radiograph is crucial but there may be difficulties, particularly in distinguishing pleural fluid from pleural thickening. Special positioning with decubitus and supine films or fluoroscopy may help to resolve these difficulties but are time-consuming, are difficult to perform in sick or elderly patients and may be unreliable (Hessen 1951). Selecting the best site for needle aspiration when fluid is loculated or the diaphragm is elevated is a problem which will be familiar to many clinicians.

Two recent advances may have much to offer in overcoming these difficulties. Computerized axial tomography has shown its superiority over plain radiography in the detection and definition of pleural abnormalities (Kreel 1976) but unfortunately can be performed in only a limited number of centres. Pleural ultrasound has much to recommend it, being simple, quick, safe, non-invasive and widely available. Pleural ultrasound has been shown to be superior to plain radiological methods in the detection of pleural fluid (Gryminski et al. 1976) and reports confirm its usefulness in detecting fluid and aiding pleural aspiration (Joyner et al. 1967; Doust et al. 1975).

In spite of these encouraging reports the technique has not gained wide acceptance. We have attempted to assess the usefulness of pleural ultrasound and report our initial experience.

Patients and Methods

Ultrasound examinations were performed using the A-mode (Ekoline 20, Smith Kline Instruments Inc.) with a 2.25 MHz transducer. The hand-held transducer has a diameter of 1.5 cm and was applied to the chest wall between the ribs, using the intercostal space as a window. A water-soluble gel was used to facilitate conductivity.

Air-filled lung transmits sound very poorly and in normal circumstances there will be only a tight cluster of high-level echoes from the chest wall and lung–pleura interface. If there is a pleural effusion the sound will be well transmitted through this fluid zone, echoes being produced at the chest wall and at the lung–pleura interface with an echo-free zone in between. The length and depth of this zone corresponds to the width and depth of the effusion. If the pleural space is occupied by a solid structure (pleural tumour or thickening)the sound is less well transmitted and echoes are produced corresponding to the size of the lesion (Figs 1–6).

The examination was usually carried out with the patient seated upright but in some very ill patients it was performed at the bedside with the patient semi-recumbent or supine. The normal side of the chest was also examined and served as a control. For recording purposes the image on the oscilloscope screen was photographed using a polaroid camera.

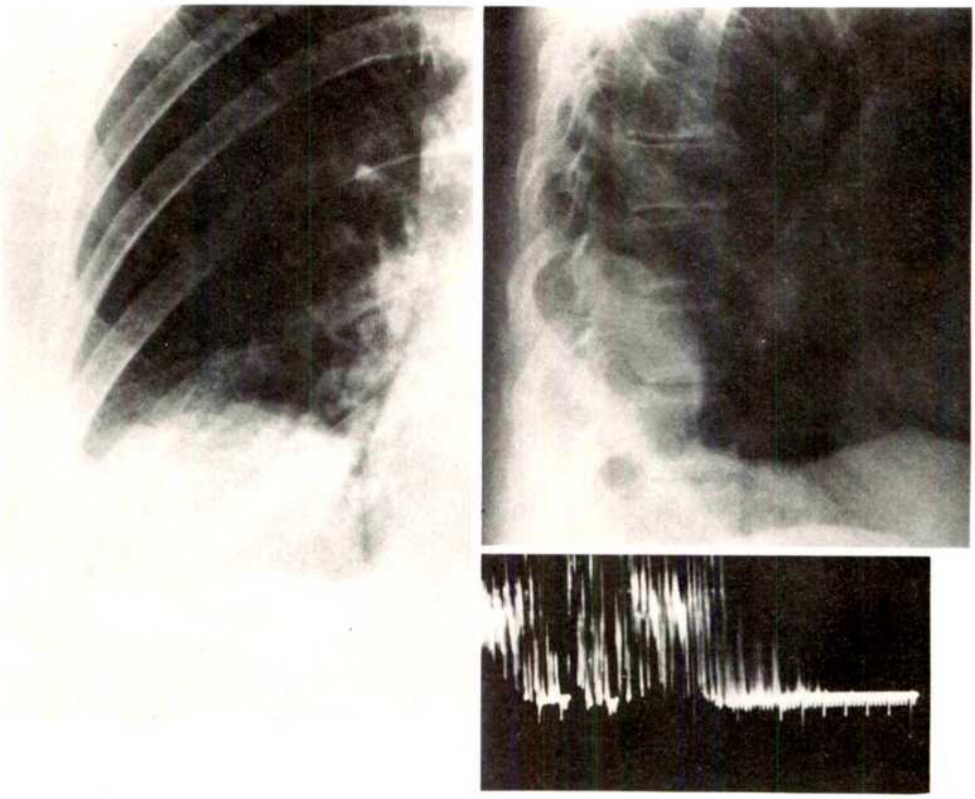

Fig. 1. A 52-year-old woman with a solid squamous cell carcinoma adjacent to the pleura. Ultrasound shows 'solid' cluster of echoes

RESULTS

We performed 78 ultrasound examinations in 62 patients during a six-month period. 27 patients had known pleural or pulmonary disease and ultrasonic examination was performed to gain experience with the technique. These patients are excluded from the

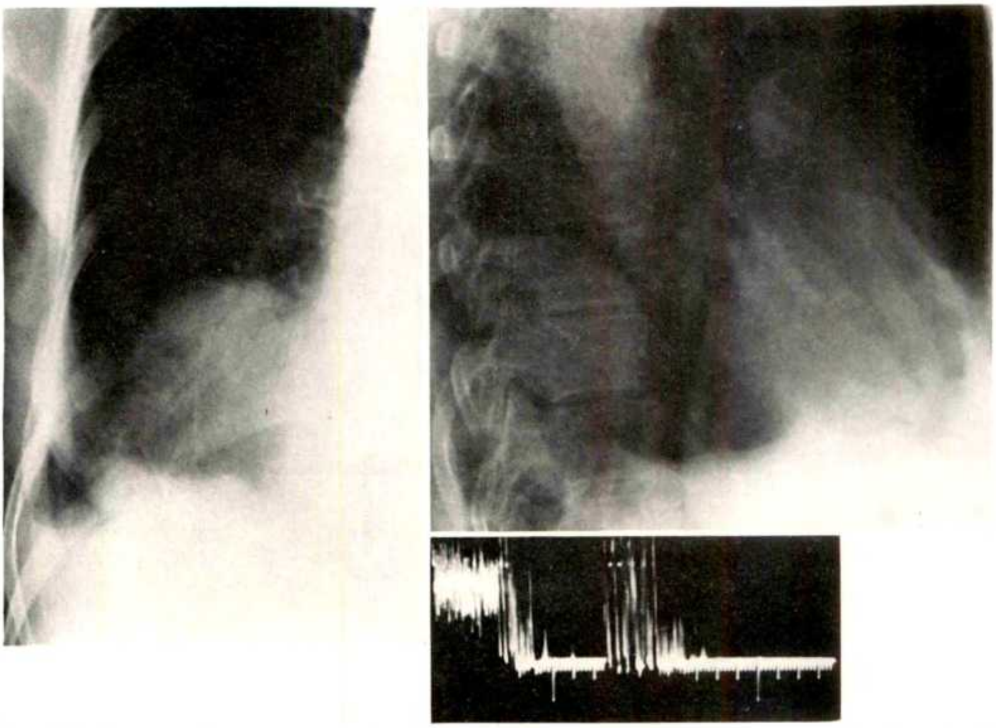

Fig. 2. A 61-year-old woman with clinical history and radiological appearances similar to those in Fig. 1. Ultrasound shows a 3 cm space separating the chest wall echoes from thickened lung–pleura interface. Aspiration yielded 30 ml of pus from a loculated empyema with subsequent complete resolution

subsequent discussion. The remaining 35 patients fell into two broad groups, those in whom ultrasound was used to locate fluid after unsuccessful attempts at aspiration and those in whom radiographic techniques and clinical examination had failed to establish whether or not pleural fluid was present.

The first group comprised seven patients in whom pleural fluid was thought to be present on the basis of clinical examination and the chest radiograph but in whom attempted aspiration had failed. Fluid was demonstrated by ultrasound in all these patients and was subsequently aspirated. In each patient the site of successful aspiration as indicated by ultrasound was different from the site of earlier aspiration attempts.

In the second group of 28 patients the radiographic findings were those of pleural disease. In nine of these patients the chest radiograph suggested the presence of pleural fluid but we were uncertain whether fluid alone accounted for the whole of the radiographic abnormality. In the remaining 19 patients it was impossible on the basis of the chest radiograph to say whether the pleural abnormality was fluid or solid or any combination of the two. The result of ultrasound examination of these groups is shown in Table I.

The ultrasonic diagnosis was correct in 33 of 35 patients. In two cases fluid was suspected from the results of ultrasound examination but was later found not to be

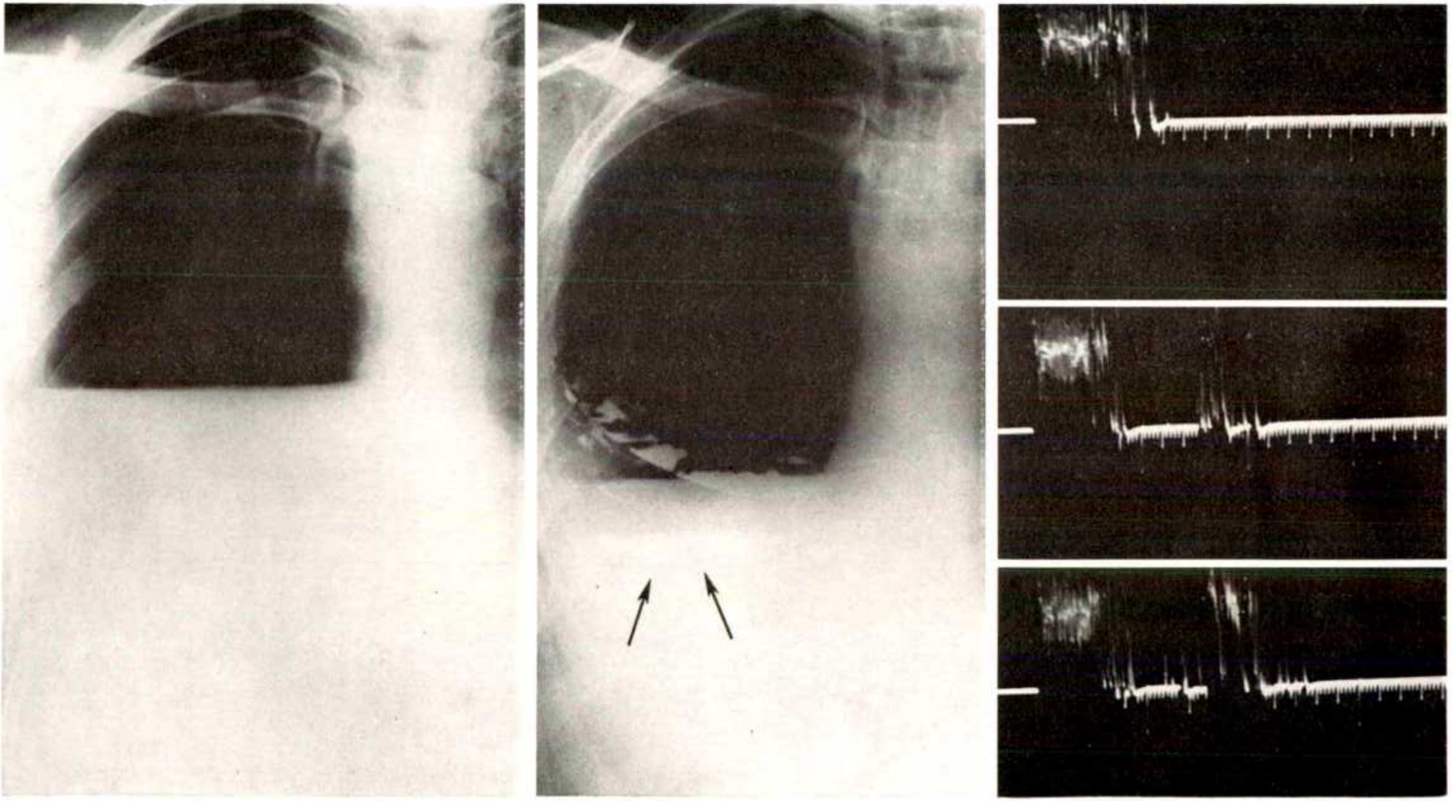

Fig. 3. A 55-year-old man with a suspected space infection after pneumonectomy. A radiograph after introduction of contrast medium defines the lower limit of the thin fluid layer and the top of the diaphragm. The top ultrasound trace shows normal chest wall echoes only; the middle trace shows fluid space between the chest wall and the top of the diaphragm and the bottom trace shows a greater number of echoes from the diaphragm

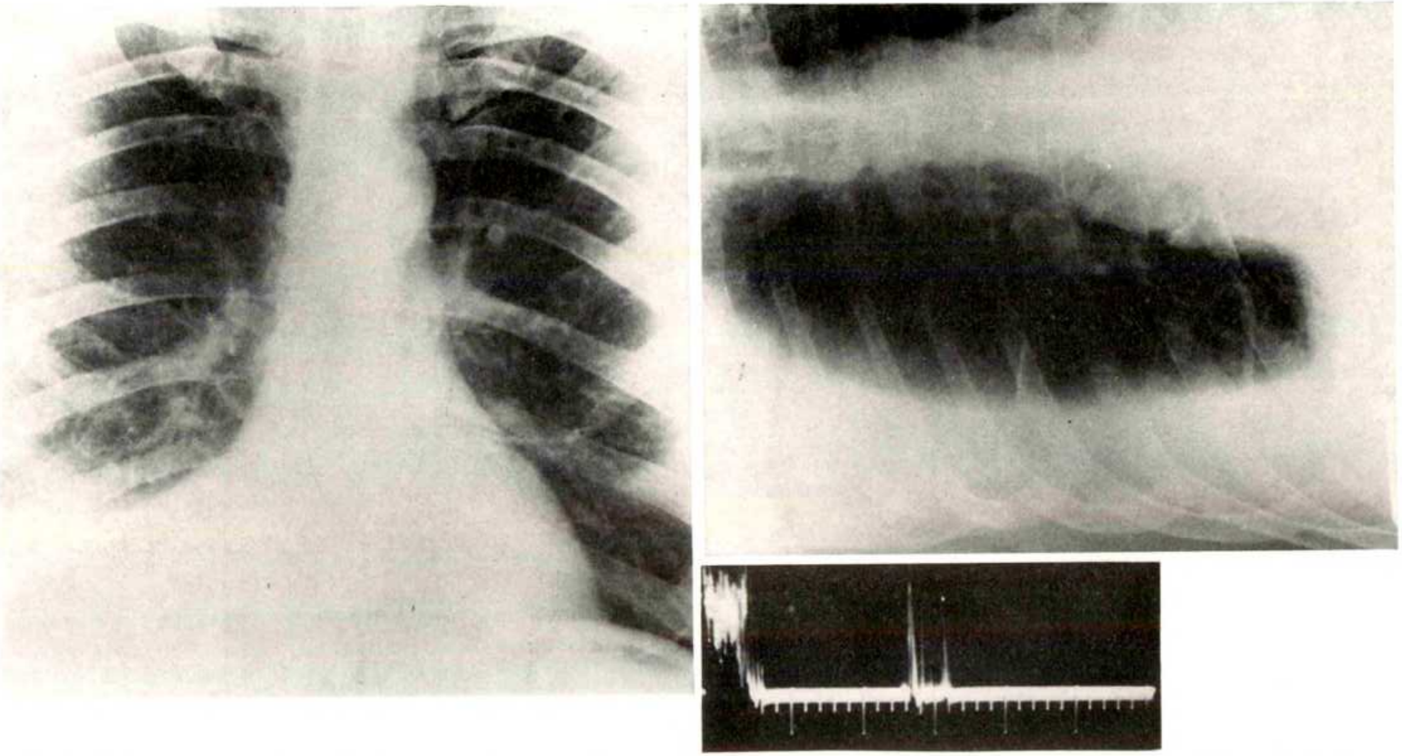

Fig. 4. A 43-year-old man with right subpulmonary effusion confirmed by fluid layer in right lateral decubitus view. Ultrasound confirms a large effusion (width of fluid layer 10 cm)

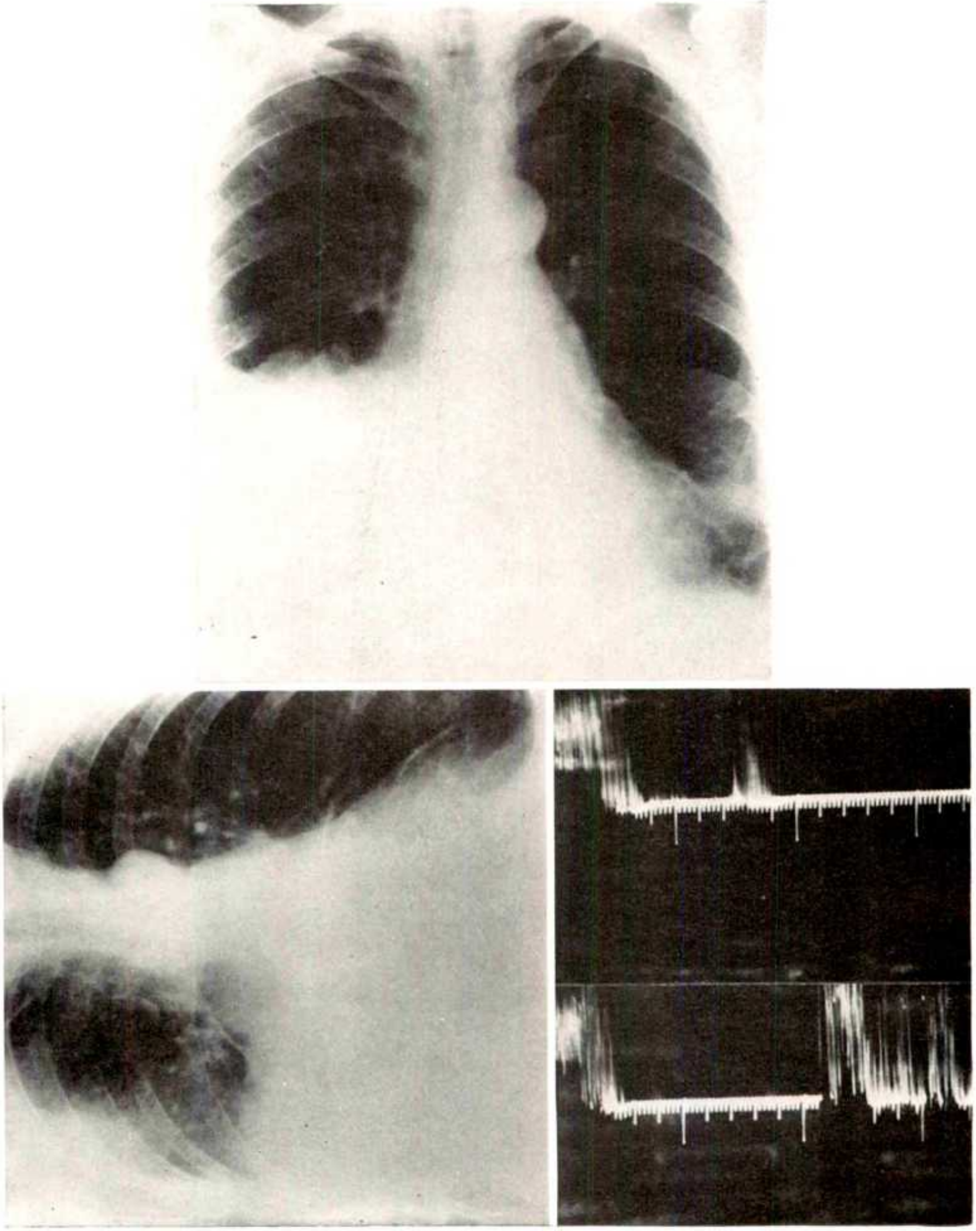

Fig. 5. Post-pneumonic effusion in 50-year-old woman which fails to layer out on right lateral decubitus radiograph. Ultrasound shows a large effusion. The top trace shows a 3 cm fluid layer separating echoes from the chest wall from echoes of the lung peripherae; and the bottom trace shows the base of the effusion with 9 cm width of fluid separating the chest wall from the diaphragm (identified by movement and greater cluster of echoes)

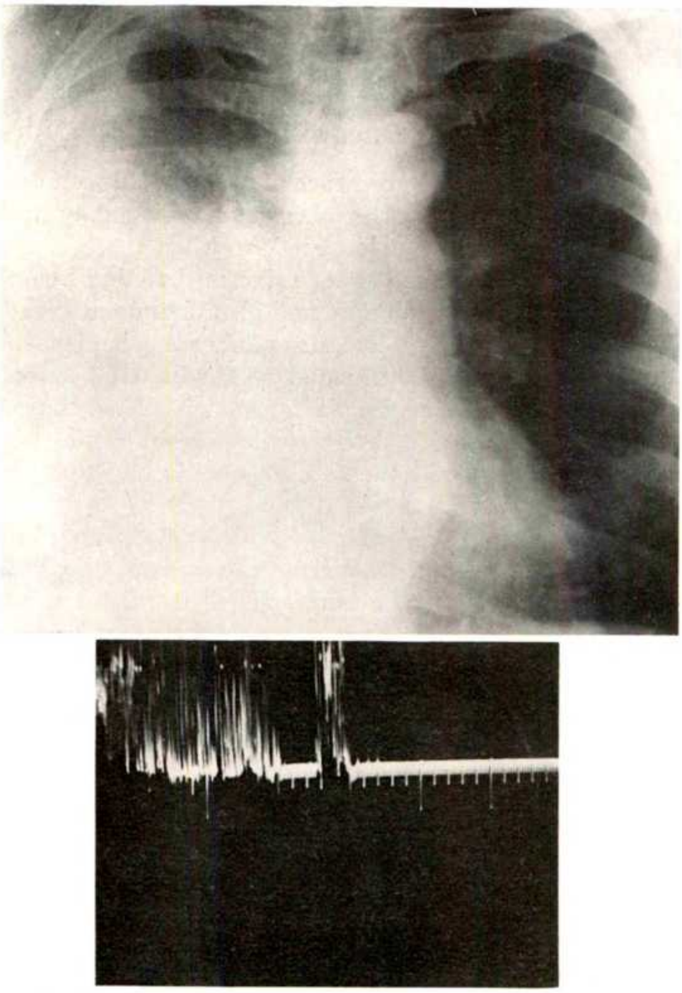

Fig. 6. A 58-year-old man with adenocarcinoma simulating mesothelioma. Ultrasound shows solid echoes from the skin (scale slightly compressed) with a small 3 cm fluid loculus at a depth of 12 cm

Table I. Comparative results in 35 patients

Diagnosis from clinical examination and chest radiograph	*Ultrasound findings*	*Results of aspiration/biopsy or thoracotomy*
Pleural effusion 7	Pleural fluid 7	Fluid confirmed 7
Impossible to distinguish fluid or solid lesions 28	Fluid 6	Fluid confirmed 4 No fluid 2
	Solid 14	Solid lesion confirmed 14
	Both 8	Both confirmed 8

present. Ultrasound examination detected fluid in all cases in which fluid was subsequently found to be present.

Discussion

Although it is possible to diagnose the presence of pleural fluid with confidence in most patients there remains a proportion of cases where chest radiography alone is inadequate. This arises particularly when fluid is loculated or when there is coexistent pleural thickening or tumour. Decubitus films are of value in detecting free pleural fluid but will not differentiate between loculated fluid and pleural tumour. Figs 1 and 2 contrast two patients with strikingly similar radiological appearances in both of whom a carcinoma was suspected on clinical grounds. Ultrasound revealed a solid lesion in one patient (Fig. 1) (bronchial carcinoma invading the pleura) and a loculated empyema in the other (Fig. 2). The empyema contained 30 ml of pus and was successfully aspirated without recourse to fluoroscopy. In this series the smallest fluid loculus that we identified with ultrasound and subsequently aspirated was 10 ml.

Unsuspected elevation of the hemidiaphragm on the side of the pleural effusion is a common cause of failed aspiration as the needle may be introduced too low. In most patients we identified the diaphragm on both sides of the chest without difficulty by means of ultrasound. It was particularly easy when fluid lay above it. Fig. 3 illustrates a patient with a suspected space infection after pneumonectomy in whom the presence of fluid was never in doubt yet repeated aspiration was unsuccessful. An unexpectedly high diaphragm was responsible for this problem as the subsequent film shows after the introduction of contrast medium. Fig. 3 also shows the differing echo patterns at the level of the fluid, and over air above and diaphragm below. The fluid could be obtained through only one critical space which was successfully identified by ultrasound.

Subpulmonary pleural fluid is sometimes difficult to diagnose from the posteroanterior radiograph alone but is usually readily demonstrated with decubitus films. However, the aspiration of such effusions may present difficulty as the fluid layer may be shallow in the erect position. Fig. 4 illustrates such a case. Ultrasound accurately located this fluid, obviating the need for several 'hit or miss' attempts at aspiration with possible risks of penetrating the liver or other viscera.

Rarely pleural effusions may fail to layer out on decubitus films and we found ultrasound invaluable in one such case (Fig. 5). The patient was treated for a pneumococcal pneumonia without the expected radiological improvement. Although the decubitus films showed no free fluid the echo pattern showed a large effusion which was successfully aspirated. The echo patterns from the top and bottom of the effusion illustrate the varying width of fluid in the chest. In this way it is possible to 'map out' an effusion and select the best possible site for needle aspiration.

Solid pleural tumours such as mesotheliomas or pleural invasion by bronchial carcinoma may pose diagnostic difficulties. Frequently multiple aspirations are attempted until sufficient failures convince the investigator of the absence of fluid. This is illustrated in Fig. 6; the accompanying echo pattern does in fact show a small fluid loculus situated at a depth of 12 cm from the skin. If the prime objective is to aspirate such fluid the prediction of depth from ultrasound could be invaluable. In this case the extra information provided by an ultrasound examination which was of greater importance was in establishing the solid nature of the pleural disease allowing us to proceed immediately to a formal biopsy with a cutting needle or drill.

In this small series we were impressed by the simplicity of the technique and by its accuracy. We were misled on two occasions. One patient had a rounded 10 cm opacity arising from the anterior mediastinum projecting into the right hemi-thorax. Ultrasound showed the presence of fluid and 300 ml was aspirated without any substantial change in the opacity on the chest radiograph. At operation a malignant thymic tumour containing a small fluid collection was found. Retrospectively we noted that the width of the fluid space on ultrasound measured only 4 cm which in site and depth could not have accounted for the size of the opacity on the chest radiograph. This error should be avoidable if careful comparison between ultrasound and chest radiograph is made.

Our second mistake was in a patient with a large mediastinal opacity. This appeared relatively echo-free on ultrasound scanning and we believed that it represented a fluid collection. The lesion was a solid, fibromyxoma of homogeneous consistency which was transonic when tested after its removal.

We selected the A-mode for this study because it is the simplest and cheapest form of ultrasound available and we found it reliable and accurate. We agree with Gryminski et al. (1976) that ultrasound may be superior to radiography in distinguishing fluid from pleural lesions although the two techniques are complementary. Ultrasound is easier than decubitus films to perform in sick patients and the technique was of great practical value in selecting the best site for aspiration of fluid.

ACKNOWLEDGEMENTS

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ENDOTHELIAL CELL PAVEMENT PATTERN IN THE PULMONARY TRUNK IN RATS IN CHRONIC HYPOXIA

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Summary

Right ventricular hypertrophy, and by inference pulmonary arterial hypertension, were induced in female Wistar Albino rats by subjecting them to a barometric pressure of 380 mmHg for four weeks. A control group was kept at normal barometric pressure for a similar period of time. The cell boundaries of the endothelial lining of the aorta, pulmonary trunk and inferior vena cava were stained in situ by a modified silver method of Poole et al. (1958). Photomicrographs of the intimal surfaces of these blood vessels at a standard magnification were used to determine the length, breadth and area of the cells. In the control rats the endothelial cells were found to have a characteristic shape and size in each of the three vessels studied. Those of the aorta were small and elongated in the direction of blood flow with tapering ends. The endothelial cells of the inferior vena cava were rectangular. Those of the pulmonary trunk were polygonal and had tessellated borders. In the test rats with right ventricular hypertrophy induced by chronic hypoxia the endothelial cell pavement pattern of the pulmonary trunk changed to resemble that of the aorta. It is considered that this was an expression of the acquired pulmonary hypertension, the fusiform shape appearing appropriate for an elevated pressure.

INTRODUCTION

Transverse sections of the pulmonary trunk yield very limited information about the endothelial cells since their cytoplasm is hardly discernible. However, staining the endothelial surface by silver salts demonstrates the cell borders and thus gives information on the size and shape of these cells both in health and disease. In previous papers we studied the normal endothelial cell pavement patterns in the aorta, pulmonary trunk, inferior vena cava and pulmonary veins (Heath & Smith 1979; Kibria et al. 1980). Subsequently we determined how the pattern in the pulmonary trunk alters when pulmonary hypertension is induced by oral administration of *Crotalaria spectabilis* seeds (Kibria et al. 1980). The present investigation was designed to determine if similar changes occur when pulmonary hypertension is induced by chronic hypoxia.

Method and Materials

Seventeen female Wistar albino rats were divided into test and control groups, the former comprising 10 animals and the latter seven. The test rats were housed in cages and put into hypobaric chambers at a reduced pressure of 500 mmHg for 24 hours. The pressure was then further reduced to 380 mmHg for 28–34 days (Table I). The animals were allowed free access to food and water and were weighed weekly. The control rats were similarly treated except that they were not subjected to a reduced atmospheric pressure.

Between Days 28 and 34 the animals were killed. They were first deeply anaesthetized with ether vapour and then the thorax and abdomen were opened by a midline incision. A small incision was made in the inferior vena cava between the origins of the renal veins and a polythene cannula was passed into the vessel towards the heart and tied firmly into place. A small incision was made in the abdominal aorta to permit the perfusate to drain off. Through the cannula in the vein each animal was perfused manually with approximately 20 ml of 5% glucose for 30 seconds until the perfusate coming through the abdominal aorta was free of blood. This was followed by perfusion for 30 seconds of 20 ml of each of the following solutions: 0.25% aqueous silver nitrate freshly prepared, 5% glucose, 3% cobalt bromide in 1% ammonium bromide, 5% glucose again and finally 10% neutral buffered formalin. The abdominal aorta was then clamped and the cannula in the inferior vena cava was connected to a reservoir of 10% neutral buffered formalin raised to a height of 25 cm above the animal's heart. From this reservoir the blood vessels of the animal were fixed for two hours.

Table I. Body weight, survival and (LV + S/RV) ratio

No.	*Initial body weight* (g)	*Final body weight* (g)	*Survival* (days)	*(LV + S)/RV*
Control				
C1	—	225	< 1	3.76
C2	—	220	< 1	4.52
C3	275	310	35	3.39
C4	270	305	35	3.72
C5	280	320	36	3.75
C6	270	330	36	3.42
C7	250	305	40	3.45
Test				
T1	250	260	28	2.10
T2	260	240	28	1.90
T3	245	260	29	1.90
T4	275	240	29	1.80
T5	250	240	29	1.96
T6	270	230	33	1.94
T7	275	220	33	1.81
T8	275	275	33	1.76
T9	210	250	34	1.79
T10	250	210	34	1.78

The thoracic inferior vena cava, thoracic aorta and pulmonary trunk were dissected out. Under the dissecting microscope the perivascular tissues were removed. Through longitudinal incisions each vessel was laid open, endothelial surface uppermost, and pinned to a sheet of cork with entomological pins. It was then dehydrated in ascending grades of alcohol, cleared in xylene and mounted on slides in DPX.

The heart and lungs were fixed separately in formol saline. The free wall of the right ventricle (RV) was dissected from the free wall of the left ventricle plus septum (LV + S) and then the two cardiac ventricles were weighed separately. The weight of the right ventricle was expressed as an inverse ratio of the weight of the left ventricle plus septum to confirm the presence of right ventricular hypertrophy, which was considered to be present when this ratio was smaller than 2.0 (Kay & Heath 1966).

From photographic prints of the endothelial surface at a standard magnification of × 1000 the lengths and breadths of the cells were measured with a ruler, the cell borders having been demonstrated clearly by the silver solution. The ratios of length to breadth were calculated in all three classes of vessels. From the same prints, cuts were made along the cell boundaries and the paper corresponding to areas of cells weighed. The areas of individual cells were calibrated from a similar photographic print of a stage micrometer taken at the same magnification. The results were compared between individual class of vessels and between test and control animals.

RESULTS

Quantitative

Table I shows the body weights, survival times and cardiac ratios of test and control animals. The test animals failed to gain weight. All the test animals, except T1, developed right ventricular hypertrophy and the mean value of (LV + S)/RV was 1.97. In contrast the mean value of left to right ventricular weight in the control animals was 3.71. By inference the test rats had developed pulmonary arterial hypertension.

Table II. Linear measurements and surface areas of endothelial cells in aorta, pulmonary trunk and inferior vena cava

Parameter	*Blood vessel*		
	Aorta	Pulmonary trunk	Inferior vena cava
Control			
No. of measurements	280	280	280
Length (μm)	63 (0.97)	41 (0.53)	62 (0.84)
Breadth (μm)	13 (0.20)	18 (0.38)	14 (0.25)
Ratio of length to breadth	4.8 (0.27)	2.3 (0.12)	4.6 (0.33)
Area (μm^2)	557 (10.25)	517 (8.20)	621 (7.41)
Test			
No. of measurements	400	400	380
Length (μm)	58 (0.64)	50 (0.58)	65 (0.89)
Breadth (μm)	14 (0.18)	13 (0.17)	16 (0.23)
Ratio of length to breadth	4.1 (0.13)	4.0 (0.15)	4.1 (0.25)
Area (μm^2)	521 (13.33)	401 (6.08)	779 (3.83)
Comparison			
Length	$t = 4.53$	$t = 11.05$	$t = 1.87$
	$P < 0.001$	$P < 0.001$	P N.S.
Breadth	$t = 2.91$	$t = 12.83$	$t = 5.93$
	$P < 0.01$	$P < 0.001$	$P < 0.001$
Ratio of length to breadth	$t = 0.86$	$t = 3.69$	$t = 0.63$
	P N.S.	$P < 0.002$	P N.S.
Area	$t = 1.95$	$t = 11.55$	$t = 5.39$
	P N.S.	$P < 0.001$	$P < 0.001$

Figures in parentheses represent the standard error of the mean.

Table II is a summary of linear measurements, areas and statistical analysis of endothelial cells in both test and control rats. Figures in parentheses indicate the standard error of the mean. With the exception of the ratio of length to breadth, all standard errors and values of 't' are calculated from individual measurements of endothelial cells. With the ratio of length to breadth, calculations are made from the mean values obtained from each animal.

The normal endothelial cell of the thoracic aorta of the rats was 63 μm in length and 13 μm in breadth with a ratio of length to breadth (LB ratio) of 4.8. It had a mean area of 557 μm^2. The endothelial cells of the pulmonary trunk were 41 μm in length, 18 μm in breadth, and had an LB ratio of 2.3; it had an area of 517 μm^2. The corresponding cells of the thoracic inferior vena cava were 62 μm in length and 14 μm in breadth, giving an LB ratio of 4.6 and an area of 621 μm^2.

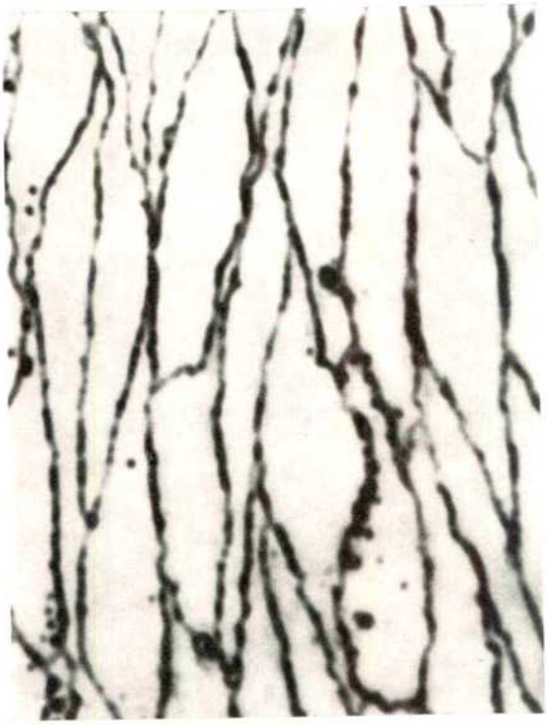

Fig. 1. Endothelial cell pavement pattern in aorta from a control rat. The cells are small and fusiform with the long axes in the direction of blood flow. Silver preparation × 700

In the test animals where the pulmonary trunk was considered to have been subjected to an increase in arterial blood pressure, the morphology of the endothelial cells changed. The mean length increased from 41 to 50 μm, while the mean breadth decreased from 18 to 13 μm. There was an associated increase in the LB ratio from 2.3 to 4.0. This is equal to that of the aorta and it is a significant change from the ratio of the controls. The mean area fell from 517 to 401 μm^2. There were significant changes between control and test rats in the area of the endothelial cells of the inferior vena cava. The area increased from 621 μm^2 in the controls to 779 μm^2 in the test rats but there was no significant change in the ratio of length to breadth.

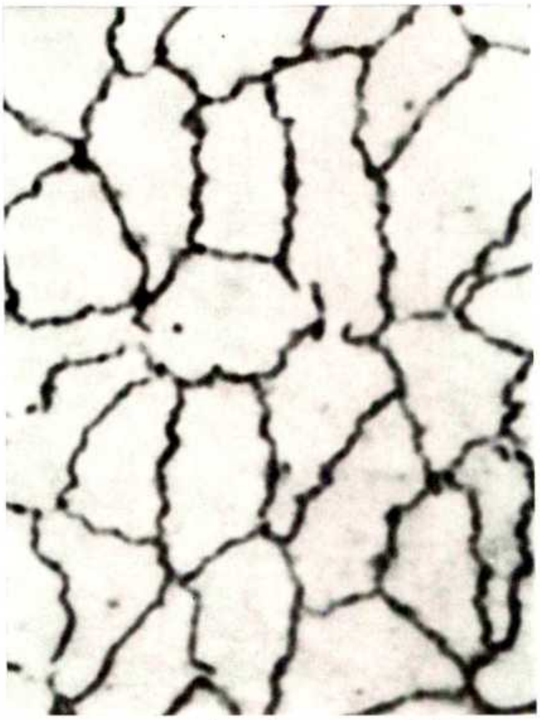

Fig. 2. Endothelial cell pavement pattern in pulmonary trunk from a control rat. The cells are polygonal and tessellated. Silver preparation ×700

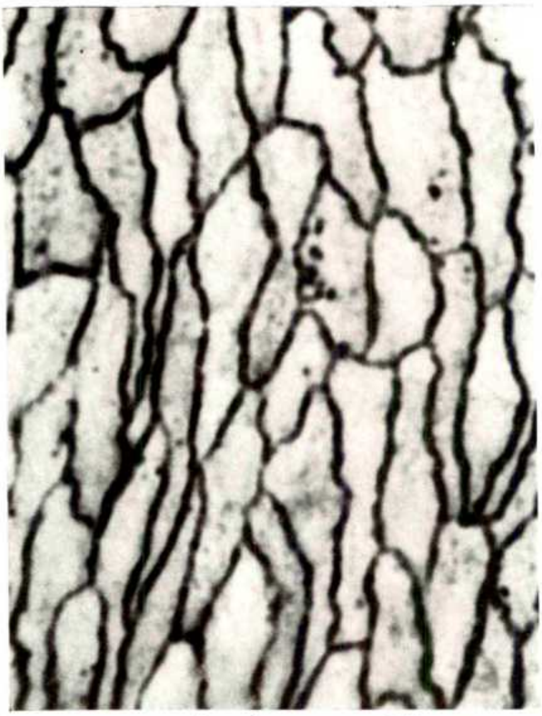

Fig. 3. Endothelial cell pavement pattern in pulmonary trunk from a test rat with right ventricular hypertrophy induced by chronic hypoxia. The cells are small and fusiform with the long axis in the direction of blood flow, thus resembling aortic endothelium. Silver preparation ×700

Qualitative

The aorta had elongated fusiform cells with tapering ends (Fig. 1) the long axes being in the direction of blood flow. The pulmonary trunk had smaller polygonal cells and their borders were tessellated (Fig. 2). They had no specific line of orientation. The endothelial cells of the inferior vena cava were also elongated but were rectangular and larger than those of the aorta. In the test animals the morphology of the endothelial cells had altered. In the pulmonary trunk they were elongated and fusiform, closely resembling those of the aorta (Fig. 3). Their long axes were orientated in the direction of blood flow. The endothelial cells of the inferior vena cava were larger but there was no change in their shape.

DISCUSSION

The results confirm our previous findings (Kibria et al. 1980) that the normal shape and size of the endothelial cell is characteristic for each of the three vessels studied. In particular the endothelial cell of the pulmonary trunk is polygonal. On exposure to pulmonary hypertension induced by chronic hypoxia, however, it changes its shape, approximately to the fusiform endothelial cell of the aorta. In a previous study we found that the same change in shape occurred in pulmonary endothelial cells in rats in whom pulmonary hypertension had been induced by feeding them on *Crotalaria spectabilis* seeds. This suggests that the fusiform shape is appropriate to a high intravascular pressure.

In our previous study employing *Crotalaria* we found that the mean area of the endothelial cells of the pulmonary trunk increased in size with the development of pulmonary hypertension (Kibria et al. 1980). This was because there was only a patchy development of small fusiform cells akin to those of the aorta. In contrast, in the present experiment the mean area of the endothelial cells of the pulmonary trunk became smaller. This was due to the much more widespread appearance of large numbers of the small fusiform cells. This difference in cell area in the two experiments may be explained on the basis of the two methods of inducing pulmonary hypertension. When using pyrrolizidine alkaloids there is a time lag before the pathological changes of pulmonary arterial hypertension occur (Kay & Heath 1966). On the other hand the pulmonary hypertension induced by hypoxia is of more rapid onset (Abraham et al. 1971). Hence in the present study the pulmonary hypertension appeared quickly and was sustained for a longer period than in the case of the raised pulmonary arterial pressure induced by the ingestion of *Crotalaria spectabilis*. Hence there was more time for the development of large numbers of small fusiform cells and these were responsible for the fall in mean area of endothelial cells.

In both the experiments employing hypoxia and *Crotalaria* seeds the endothelial cells of the inferior vena cava became larger in the test rats. It is likely that in both experiments this was because this vessel became distended when the animal developed congestive cardiac failure.

In native highlanders with pulmonary hypertension from birth due to the hypoxia of high altitude the elastic configuration of the media of the pulmonary trunk remains for some years similar to that of the aorta (Heath & Williams 1977). In this paper we provide evidence that in states of chronic hypoxia a similar conversion from pulmonary to aortic configuration occurs in the endothelium of the pulmonary trunk.

ACKNOWLEDGEMENTS

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Requests for reprints to Dr P. Smith, Department of Pathology, Duncan Building, Royal Liverpool Hospital, Liverpool L7 8XW.

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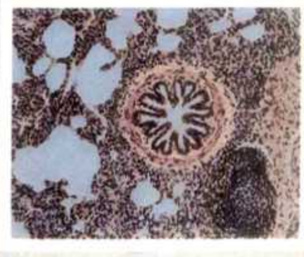

Cross-section of bronchiole illustrating bronchospasm due to contraction of respiratory smooth muscle.

> "Why are so many asthma patients treated with oral drugs when their symptoms could be more effectively controlled, and with much less risk, by therapy administered by inhalation? ... All patients with asthma should be treated with a bronchodilator aerosol, and it is rational to use only the more selective sympathomimetic drugs..."
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PRODUCT INFORMATION

PRESENTATION AND BASIC NHS COST

Ventolin Inhaler is a metered-dose aerosol delivering 100mcg salbutamol BP per actuation. Each canister contains 200 inhalations. Basic NHS cost £3·00.
Ventolin Rotacaps 200mcg & 400mcg each contain a mixture of the stated amount of microfine salbutamol BP (as sulphate), and larger particle lactose in light blue/colourless or dark blue/colourless hard gelatine cartridges, respectively. Containers of 100. Basic NHS cost £5·29 and £7·15 respectively.
Ventolin Rotahaler for use in conjunction with Ventolin Rotacaps. Basic NHS cost 78p.

INDICATIONS

Routine control of bronchospasm in bronchial asthma, bronchitis and emphysema, or as required to relieve attacks of acute bronchospasm. Doses may also be taken before exertion to prevent exercise induced asthma or before exposure to a known unavoidable challenge.

DOSAGE AND ADMINISTRATION

As single doses for the relief of acute bronchospasm, for managing intermittent episodes of asthma and to prevent exercise-induced bronchospasm.
Using Ventolin Inhaler – *Adults:* one or two inhalations.
Children: one inhalation increasing to two if necessary.
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For optimum results in most patients inhaled Ventolin should be administered regularly.

CONTRA-INDICATIONS

Ventolin preparations should not be used for the prevention of threatened abortion.

PRECAUTIONS

If a previously effective dose of inhaled Ventolin fails to give relief lasting at least 3 hours, the patient should be advised to seek medical advice. Ventolin should be administered cautiously to patients suffering from thyrotoxicosis. Unnecessary administration of drugs during the first trimester of pregnancy is undesirable.

SIDE EFFECTS

No important side effects have been reported following treatment with inhaled Ventolin.

PRODUCT LICENCE NUMBERS

Ventolin Inhaler 0045/5022; Ventolin Rotacaps 200mcg 0045/0116;
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PRODUCT INFORMATION

PRESENTATION AND BASIC NHS COST

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£9·67 respectively.
Becotide Rotahaler, for use in conjunction with Becotide Rotacaps. Basic NHS cost 78p.

INDICATIONS

Bronchial asthma especially in patients whose asthma is not adequately controlled by bronchodilators and patients with severe asthma who would otherwise be dependent
systemic corticosteroids or adreno-corticotrophic hormone (ACTH) or its synthetic equivalent.

DOSAGE AND ADMINISTRATION

Using Becotide Inhaler – *Adults:* two inhalations three or four times a day is the usual maintenance dose. In severe cases dosage may be started at twelve to sixteen inhalatio
per day and subsequently reduced when the patient begins to respond.
Children: one or two inhalations, two, three or four times a day according to the respon
Using Becotide Rotahaler – *Adults:* one 200mcg Becotide Rotacap three or four time
a day is the usual maintenance dose.
Children: one 100mcg Becotide Rotacap, two, three or four times a day according to the response.
For optimum results inhaled Becotide should be administered regularly.

CONTRA-INDICATIONS

No specific contra-indications to inhaled Becotide are known but special care is necess
in patients with active or quiescent pulmonary tuberculosis.

PRECAUTIONS

The maximum daily intake of beclomethasone dipropionate BP should not exceed 1mg
Inadequate response after the first week of inhaled Becotide therapy suggests that excessive mucus is preventing penetration of inhaled drug to the target area. A short co
of systemic steroid in relatively high dosage should be given and therapy with inhaled Becotide continued.
Unnecessary administration of drugs during the first trimester of pregnancy is undesir
When transferring patients to Becotide from systemic steroid therapy the possibility of adrenocortical suppression should be considered and patients given a supply of oral steroids for use during periods of stress. Please refer to the detailed procedure describ
the data sheets for Becotide Inhaler and Becotide Rotacaps.

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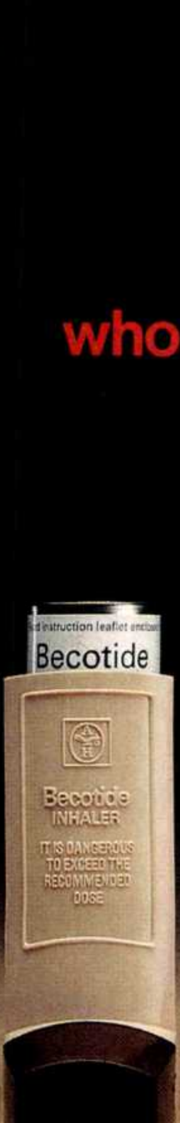

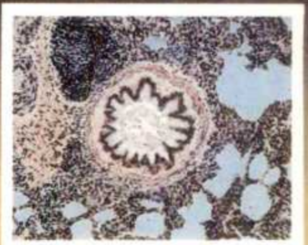

Cross-section of bronchiole illustrating bronchospasm complicated by bronchial mucosal oedema and hypersecretion of mucus.

“To support this claim of extraordinary activity (of Becotide), there are not only statistically valid comparisons but also numerous validated individual experiences. These include the impressive therapeutic results in patients with severe asthma not controllable with high daily doses of systemic steroids; the beneficial responses of those refractory to adrenergic agonists and unable to tolerate even suboptimal doses of theophylline; the suppression of asthma unresponsive to mediator-release inhibitors, such as cromolyn sodium; and, importantly, the high level of acceptance and compliance among people who do not comply with other standard therapeutic routines.”

(*Lancet*, 1979, **i**, 932-933)

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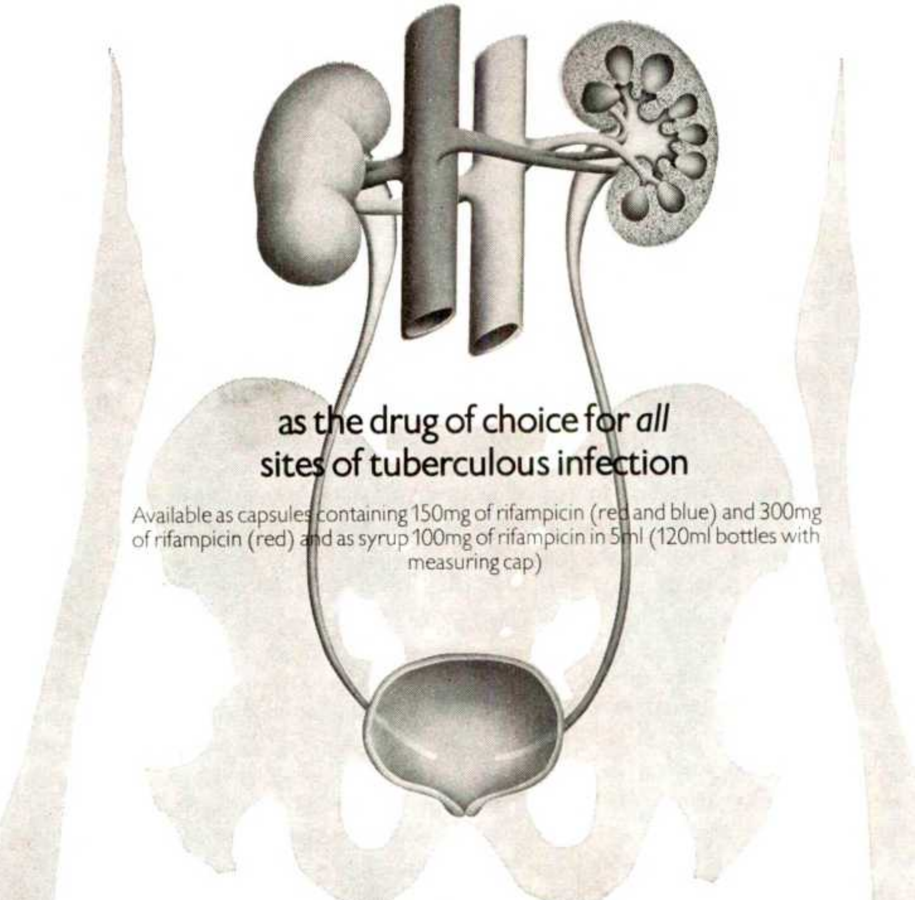

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Br. J. Dis. Chest (1980) *74*, 369

TUBERCULOSIS OF SUPERFICIAL LYMPH NODES

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Willesden Chest Clinic, London

Summary

A retrospective survey of all patients with superficial lymph node tuberculosis in the London Borough of Brent notified between 1972 and 1976 is reported. There were 239 patients, of whom 79% were of Afro-Asian or Indo-Asian origin. The annual number of cases increased from 28 in 1972 to 69 in 1976. Of immigrant patients 75% developed the disease within five years of entry to the country. The nodes affected were overwhelmingly cervical or supraclavicular (93%) and in 80% only the superficial lymph nodes of the neck were involved. Treatment was with chemotherapy, latterly with rifampicin and isoniazid for nine months with initial ethambutol. Initially surgery was commonly used to confirm the diagnosis (85% in 1972) but much less often by 1976 (49%). In no case, when a clinical diagnosis had been made, was that diagnosis found to be wrong on subsequent biopsy. Only four relapses were recorded in a follow up period of up to four years.

INTRODUCTION

Although tuberculosis has become less common in the United Kingdom over the last 25 years (Citron 1973), the incidence has recently risen in areas with a high immigrant population (British Thoracic and Tuberculosis Association 1973; Prowse & Cavannagh 1976; British Thoracic Association 1978). Where this has occurred, non-pulmonary disease is also seen relatively frequently. We have reviewed our experience over the years 1972–6 inclusive in the Brent Health District. There were 239 notifications of superficial lymph node disease out of a total of 1252 notifications of tuberculosis.

Patients and Methods

A retrospective study was made of records of all patients with tuberculous lymph node disease notified between 1972 and 1976. Of the 239 notified, 194 cases had been seen and treated at the Willesden Chest Clinic or Central Middlesex Hospital (81%). 45 (19%) were seen and treated at neighbouring centres. Both in our own service and at other hospitals several physicians and surgeons were involved in the care of the patients and no uniform pattern of management was adhered to, although we aimed to give full, unsupervised, chemotherapy. Follow-up supervision was variable. Of the 239 patients initially notified 55 (23%) have been lost to follow-up. This figure is high and may be explained by the mobility of the immigrant community and by treatment at more than one centre.

Incidence

In the five-year period during which the 239 cases of superficial lymph node tuberculosis were notified, a total of 1252 notifications of tuberculosis was made. Superficial lymph node disease constituted 19% of all notifications during this period. However, as shown in Table I, not only has the absolute incidence of superficial lymph node disease risen from 28 in 1972 to 69 in 1976, but the proportion of tuberculosis presenting as superficial lymph node disease has increased from 15.9 to 23.3%.

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Characteristics of patients

The age of the patients at the time of diagnosis is shown in Table II. The disease is one of young adults, with 54% of the patients being between 20 and 40 years of age. It is relatively uncommon at the extremes of life.

The vast majority of patients were of Asian origin, either coming directly from the Indian sub-continent or from Asian communities in Africa. Overall there is a small preponderance of women (57%). In elderly patients more were of European origin and more were female. 13 of the 16 patients aged over 60 were women, of whom nine were Europeans. Details of the place of birth are shown in Table III. Length of stay of immigrant patients in this country before diagnosis is shown in Table IV. Three-quarters of the patients were diagnosed within five years of their entry to the United Kingdom.

Table I. Incidence of lymph node tuberculosis

	Tuberculous lymph nodes	*Total tuberculosis notifications*	*Nodes as % of total*
1972	28	176	15.9
1973	38	246	15.4
1974	50	244	20.5
1975	54	290	18.6
1976	69	296	23.3
Total	239	1252	

Table II. Age and sex of 239 patients (43% male) with superficial lymph node disease

Age	*No.*
0–9	12 (5.0%)
10–19	21 (8.8%)
20–29	62 (25.9%)
30–39	69 (28.9%)
40–49	33 (13.8%)
50–59	26 (10.9%)
60+	16 (6.7%)

Site of disease

Cervical and supraclavicular nodes were nearly always involved (94%). Involvement of more than one site was relatively uncommon, a single site being involved in 80% of the cases. Complicating pulmonary parenchymal disease was uncommon, being present in only 16 patients. Details of the site of disease are shown in Table V.

Diagnosis and treatment

In the first three years under review, over 80% of the patients underwent a surgical procedure, either excision or biopsy of the nodes. In all patients in whom a positive culture was obtained from the nodes, the organism was found to be *Myco. tuberculosis* var. *hominis*, fully sensitive to all

Table III. Place of birth of patients with superficial lymph node tuberculosis

Place of birth	*No.*		
United Kingdom	15		(6.3%)
Europe	9		(3.7%)
Afro-Asia	101	188	(78.6%)
Indo-Asia	87		
West Indies	9		(3.7%)
Other and not known	18		(7.7%)

the major antituberculous drugs. A policy of routine biopsy was abandoned in the last two years and diagnosis was made on clinical grounds. Surgery was reserved for those who did not improve on chemotherapy within the first two months of treatment. Eight patients (17.4%) required biopsy out of a total of 46 in whom a clinical diagnosis had been made and in no case did biopsy show that the clinical diagnosis was wrong.

Our aim has been to give all patients a full course of antituberculous chemotherapy. In 1973 the standard regimen was isoniazid and PAS for 18 months with an initial three months of triple therapy with streptomyomycin. In 1973 ethambutol was substituted for PAS and from 1974 rifampicin was increasingly used in place of streptomycin. By 1975 rifampicin and isoniazid for nine months with the addition of ethambutol for the first three months had become our standard regimen. Corticosteroids were not used. Compliance was initially monitored by urine testing for PAS, but subsequently by interrogation of the patient.

Table IV. Duration of stay in the United Kingdom before diagnosis of superficial lymph node tuberculosis

Duration of stay (years)	*No.*	*Cumulative* %
0–2	87	40.5
3–5	75	75.4
6–10	34	91.2
10+	19	100

The duration of stay was not known in nine patients and 15 were born in the United Kingdom.

Table V. Site of disease

Site of disease	*No.*	
Cervical/supraclavicular nodes	224	(93.7%)
Axillary nodes	20	(8.3%)
Other nodes	3	(1.2%)
Evidence of other tuberculous disease		
Pulmonary parenchyma	16	(6.7%)
Mediastinal	22	(9.2%)
Other (e.g. bone)	5	(2.1%)
No. of sites involved		
One site	192	(80.3%)
Two sites	44	(18.4%)
Three sites	3	(1.2%)

RESULTS

By the end of the period of chemotherapy, the lymph nodes had regressed in all of the patients. More than 90% of patients have completed a full course of chemotherapy. In the five-year period under study only four patients are known to have relapsed at various times after treatment. None of these patients had been treated with rifampicin and isoniazid. Two were thought to be poorly compliant with medication. The minimum follow-up period has been one year.

DISCUSSION

In the last ten years, notifications of tuberculosis in Brent have risen considerably. This rise in notifications has been particularly striking for non-pulmonary tuberculosis, which is predominantly due to superficial lymph node tuberculosis. The increasing incidence of lymph node tuberculosis appears to be part of a pattern of increase in a vulnerable immigrant population.

In this population, unlike previously reported series (Wilmot et al. 1957; Mair & Elverland 1975) in European patients, we have found the incidence to be highest in young adults. The absence of disease at the extremes of life is striking. This may in part reflect the age and sex structure of the immigrant community which is not known. The majority of our patients presented with the disease within five years of entry to the United Kingdom. The pattern is similar to that seen with pulmonary tuberculosis. The response to treatment has thus far been satisfactory with a relapse rate of under 2% on follow-up of one year.

As several different physicians and surgeons have been involved in the care of these patients, the therapeutic approach has not been standardized except that all received chemotherapy, with the objective of giving all patients a full course of drugs, which has in general been achieved. Our study does not permit us to assess the relative importance of surgery, but it does not appear that this has made any substantial contribution to cure. In view of this, and the fact that in no case has the clinical diagnosis of superficial lymph node tuberculosis, supported by the presence of a positive tuberculin test, been found to be erroneous, current policy is based on clinical diagnosis and chemotherapy. Biopsy is reserved for patients failing to respond, including the small proportion of patients in whom lymph nodes enlarge during chemotherapy. We have proceeded to biopsy in less than 20% of those in whom a clinical diagnosis has been made. This is lower than the biopsy rate in group C of Campbell and Dyson's (1977) study, although similar to their overall rate of 'second-look' surgery.

While the presence of cervical lymphadenopathy in any young adult raises the possibility of lymphoma or other more serious disorder, in recent immigrants of Asian origin no patient who has initially been notified and treated as tuberculosis has had the diagnosis subsequently changed. We believe that our present approach based on chemotherapy and selective biopsy is safe. Chemotherapy is an effective method of treatment for tuberculosis of the superficial lymph nodes in our community.

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ACTIVE PULMONARY TUBERCULOSIS DISCOVERED AT POST-MORTEM EXAMINATION OF THE LUNGS OF BLACK MINERS

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Summary

The prevalence of active pulmonary tuberculosis and pneumoconiosis in black mine workers who died while working on mines and came to autopsy is reported.

All black mine workers are regularly examined radiologically during life and those with pulmonary tuberculosis or pneumoconiosis are compensated and sent home (after treatment in the case of tuberculosis) and would not enter this autopsy series.

Details are given of the prevalence of tuberculosis separately for gold, coal and asbestos miners. Tuberculosis was age-related in all three cases.

In black gold miners the presence of a slight degree of silicosis not detected radiologically in life was associated with a significantly increased prevalence of pulmonary tuberculosis compared to gold miners without silicosis.

This was not found to be the case in those in whom asbestosis or coal workers' pneumoconiosis was found at autopsy.

INTRODUCTION

Morbidity from pulmonary tuberculosis is still important among black mine workers, nearly 5000 cases being certified by the Medical Bureau for Occupational Diseases in 1976. About 600 000 black men work on the mines, with a high rate of labour turn-over. Black miners are recruited from several countries in southern Africa and many are resident outside South Africa.

Persons with tuberculosis discovered at initial examination are not employed and those discovered at subsequent examination are treated and compensated, and would therefore enter this post-mortem study only if they died while being treated in a mine hospital. Blacks with radiologically detectable pneumoconiosis are forbidden to continue work in a dusty atmosphere. They are compensated and usually return to their homes and would not therefore enter this study group.

The heart and lungs of all black miners who die while employed by a mine are removed subject to permission from the next of kin and the organs are examined by specialist pathologists at the National Research Institute for Occupational Diseases, whose reports are referred to a Compensation Committee. Compensation is given for even a minimal degree of pneumoconiosis and under certain circumstances for active tuberculosis.

Over half the deaths were due to accidents, violence and other causes of relatively sudden death.

The purpose of this report is to examine the prevalence at autopsy of active pulmonary tuberculosis in this regularly screened black population working in different kinds of mines and to determine whether relatively minor degrees of pneumoconiosis have any effect on the prevalence of tuberculosis.

Method

The reports on the autopsy findings in the heart and lungs of all black miners who died in South Africa between 1 January 1974 and 1 January 1978 and who were working in large gold, coal or asbestos mines at the time of death were reviewed.

3778 cases referred by large gold mines, 1251 referred by coal mines and 247 referred by asbestos mines were reviewed.

Only the 95% of all cases where an estimate of age was available were considered in this paper.

A large number of the deceased workers will have worked on other kinds of mines than those where they died. Reliable details of such previous service were not available or were too fragmentary to be of value.

Black miners have a chest radiograph at the beginning of each contract and periodically at intervals of nine months or less, during the contract. The active tuberculosis lesions found at autopsy are therefore those which were not apparent at the time of the last radiograph and any small lesions which had been 'missed' by the medical officers viewing the films. In many of the cases with active pulmonary tuberculosis lesions death had been the result of tuberculosis, usually from the pulmonary lesion, but in a few cases from tuberculous meningitis, pericarditis or peritonitis.

The examination of the lungs is carried out in a standardized manner by a team of pathologists in a research institute (Goldstein, personal communication).

The lungs are sliced from lateral to medial borders at least four times, and often more, and are then inspected and palpated and suspect areas are excised for histology. In all cases three blocks are taken from each of three zones in each lung. Hilar and other lymph glands are incised and inspected and sections are taken from at least one gland on each side.

Active tuberculosis is defined according to the following criteria: non-encapsulated caseation; encapsulated caseation only if there is a non-granular cell reaction on the periphery or polymorphonuclear cell infiltration into the caseous material; acute inflammatory reaction showing the presence of acid-fast bacilli; and tuberculous follicles.

The demonstration of acid-fast bacilli is not required except in case of acute inflammatory reaction. Slight 'asbestosis' is diagnosed histologically when collagen appears around the respiratory bronchioles and is associated with asbestos bodies or fibres. Slight coal workers' pneumoconiosis is diagnosed when a 'significant' amount of collagen appears in foci of coal dust reticulination. Silicosis is diagnosed when foci of dust reticulination are present in which a significant amount of collagen is present. In a large number of cases the presence of quartz dust was demonstrated. These criteria have not changed in the last twenty years.

RESULTS

Table I shows the prevalence of active tuberculous lesions in the lungs examined in three age groups for the three kinds of mining during the period 1 January 1974 to

Table I. Prevalence of active pulmonary tuberculosis discovered at post-mortem of black miners. (1974–8)

Age (years)	*Asbestos miners*	*Coal miners*	*Gold miners*
17–29	3/61 (5%)	7/354 (2%)	65/1627 (4%)
30–49	11/126 (16.6%)	58/662 (9%)	85/1678 (5%)
50 +	10/60 (16.6%)	31/235 (13.2%)	47/473 (9.9%)
Total	24/247 (9.7%)	96/1251 (7.7%)	197/3778 (5.2%)

1 January 1978. It is apparent that the prevalence of active tuberculous lesions increases with age in all the types of mining exposures studied.

Table II shows that an important proportion of the tuberculous lesions reported at autopsy were the direct cause of death. This is especially true of the asbestos miners.

Table III shows the influence of the presence of pneumoconiosis on the prevalence of tuberculosis. Only in the case of silicosis is there a significant influence ($P < 0.001$).

The asbestos and coal groups are not subdivided into age categories as the numbers with tuberculosis in some of the groups are very small.

Table II. Tuberculosis as cause of death

Miners of	*Deaths*
Asbestos	17/24 (70.8%)
Coal	37/93 (39.7%)
Gold	87/198 (43.5%)

Table III. Prevalence of tuberculosis in relation to the presence of pneumoconiosis

	Age			
	17–29	30–49	50+	Total
Asbestos miners				
Asbestosis				10/100 (10%)
No asbestosis				14/147 (10%)
Coal miners				
Coalworkers' pneumoconiosis				7/97 (7%)
No coalworkers' pneumoconiosis				89/1154 (7.7%)
Gold miners				
Silicosis	7/35 (20%)	22/263 (8%)	21/151 (13.2%)	50/449 (11.1%)
No silicosis	58/1592 (3.6%)	63/1415 (4.4%)	26/322 (8.1%)	147/3329 (4.4%)
P	<0.001	<0.001	<0.05	<0.001

DISCUSSION

There are no reports of the prevalence at autopsy of active pulmonary tuberculosis in regularly screened populations and there is very little information on the prevalence in unscreened black populations and none relevant to the present decade.

Medlar (1948) included American blacks in his classic studies on the prevalence of minimal pulmonary tuberculosis in persons who died suddenly and whose lungs were examined in detail. He found that 8.4% of 131 blacks in the 20–39 year age group and 9.2% of 95 in the 40–59 year age group had tuberculosis. The criteria used for the autopsy diagnosis differed from ours in that a total of at least 1 cm^3 of lung parenchyma had to be involved. He also included calcific foci without caseation which was not done in this study, but there were few of these. His findings relate to the position in the USA 30 years ago.

Braun (1953) published a report on the prevalence at autopsy of active tuberculosis in Lagos (Nigeria) in blacks of all ages, the large majority of whom had died suddenly or undiagnosed. He defined no criteria for the diagnosis. He found that 12% of 5429 autopsies carried out in the years 1945 to 1952 revealed active tuberculous lesions. This prevalence is similar to that found in this study.

In the present study the autopsy prevalence of pulmonary tuberculosis increased with age (Table I). This is well known for white populations. It has been shown to be the case for living black miners on South African gold mines (Laing 1967), and it also applies to the general living black population of South Africa (Küstner 1979).

The differences in autopsy prevalence among the three types of mines probably reflects little more than the epidemiology of tuberculosis in their areas of black labour recruitment. There are important local geographical variations in the incidence of tuberculosis in the region of southern Africa (Laing 1967). The expertise of readers of radiographs on some smaller coal and asbestos mines is also not likely to measure up to the high standard of the full-time medical officers of large gold mines. Living conditions on coal and asbestos mines are sometimes inferior to those on gold mines and this might be a factor influencing the prevalence of tuberculosis.

Table II shows that these tuberculous lesions are frequently the cause of death, although the subjects had had chest radiographs at least every nine months, usually on 100 mm films, but sometimes on 70 mm or large films. Tuberculosis may still run a very acute course in blacks and not uncommonly progresses to an irremediable stage in nine months. As, in general, only one reader reads the films, some of these advanced cases may have arisen from minor infiltrates that were overlooked. It is not rare, however, to see men with advanced pulmonary tuberculosis whose film taken less than nine months previously is entirely normal.

The death rate is particularly high in the case of the asbestos miners. One can only speculate on the reason for this. Systemic immunological changes occur in asbestos exposed persons (Miller 1978) and this is a possible factor. It appears that tuberculosis was frequently present at post-mortem in persons suffering from asbestosis 30 or 40 years ago in the United Kingdom, but that this is no longer the case (Smither 1965). In Germany during the same period the prevalence was much lower (Bohlig et al. 1960), though probably excessive.

Table III shows that the presence of silicosis in gold miners is clearly associated with an increased prevalence of active pulmonary tuberculosis but that this is not the case for coal workers' pneumoconiosis or asbestosis. The silicosis was usually of very minor degree (a single nodule found in the sections of lung being a sufficient criterion for diagnosis) and in the vast majority the radiographs were therefore normal or showed abnormalities slight enough to be missed. Of the 449 cases of silicosis among the gold miners, only 11 were considered to be of 'moderate' degree and three marked. There was no case of massive fibrosis. When these 14 cases are removed from the sample of 449 silicotics the excess of tuberculosis remains unchanged in magnitude. The coexistence of silicosis and tuberculosis in gold miners was associated with a significant but small increase in the proportion of deaths in comparison with deaths from tuberculosis in the absence of silicosis (28/50 *vs.* 59/148; $P < 0.05$).

Cases of silicosis also occurred among coal and asbestos miners. These may have arisen as a result of previous exposure to high silica dust in gold mines, but could also have arisen in the coal and asbestos mines themselves under certain mining conditions. There were 82 such cases among coal miners (only one case was considered to be of 'moderate' severity and none 'marked'). Sixteen (19.5%) of these had concurrent pulmonary tuberculosis. Among the asbestos miners there were 21 cases of silicosis, of whom six (29%) had concurrent tuberculosis. These findings underline the specific nature of the relationship between silica dust and active tuberculosis.

Among coal miners the presence of coal workers' pneumoconiosis did not give rise to an excess of active tuberculous lesions. This may be because all the cases of coal workers' pneumoconiosis except one were of slight degree. Chatgidakis, who in 1963 surveyed the autopsy of South African black coal workers who died during the period 1958 to 1961, found active tuberculosis in 21% of 253 cases of coal workers' pneumoconiosis. Her series, however, contained more cases with more severe grades of the disease (there were 17 cases of massive fibrosis).

While the association of pulmonary tuberculosis with coal workers' pneumoconiosis was documented by autopsy studies 30 years ago (Gooding 1946) and is also reported in living coal miners by Meiklejohn (1960), Fritze (1975) and Theodos and Gordon (1952). Cochrane et al. (1956) found that the attack rate of pulmonary tuberculosis was increased only in older age groups and only when category two or three coal workers' pneumoconiosis was present. He did, however, include cases of progressive massive fibrosis. It would seem that slight degrees of coal workers' pneumoconiosis, unlike slight degrees of silicosis, are not associated with excess tuberculosis.

In the asbestos miners the presence of asbestosis (although 28 of the 100 cases were more than slight) had no effect on the prevalence of tuberculosis.

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AMOXYCILLIN VERSUS AMPICILLIN IN TREATMENT OF EXACERBATIONS OF CHRONIC BRONCHITIS

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Summary

To compare the efficacy and unwanted effects of amoxycillin and ampicillin in the treatment of acute exacerbations of chronic bronchitis, 199 patients were recruited from 28 centres into a double-blind between-patient comparison of four regimens: ampicillin 250 mg or 500 mg, amoxycillin 250 mg or 500 mg, each given orally three times daily for seven days. In these doses, amoxycillin and ampicillin were equally effective and there was no apparent advantage in using the higher dose of either drug in preference to the lower dose. Unwanted effects were few. Only in five patients did diarrhoea lead to withdrawal of therapy and there was no significant difference between the two drugs in this respect. Rashes occurred in four patients, all on ampicillin.

INTRODUCTION

Amoxycillin is a semi-synthetic penicillin with some advantages over ampicillin. Gastrointestinal absorption is better and is unaffected by food (Croydon & Sutherland, 1970) and in chronic respiratory infections it gives high intrabronchial antibiotic levels when the sputum is no longer purulent, unlike levels of ampicillin which decline as sputum purulence decreases (May & Ingold 1973). Amoxycillin has therefore been claimed to be more effective than ampicillin in the treatment of acute on chronic bronchitis. The use of amoxycillin in preference to ampicillin has been criticized as being more expensive and there is no evidence from trials directly comparing the two drugs to support the claim of clinical superiority. The British Thoracic Association has carried out a study to compare the efficacy and unwanted effects of amoxycillin and ampicillin in the treatment of exacerbations of chronic bronchitis. The two drugs have very similar half-lives in plasma after oral administration (Brusch et al. 1974), so both drugs were given three times daily.

Patients and Methods

One hundred and ninety-nine patients entered the study from 28 centres. Those eligible for entry were in-patients over 18 years of age, with chronic bronchitis (MRC criteria) admitted with an exacerbation and having purulent or mucopurulent sputum. Those who had already received five days or more of amoxycillin or ampicillin, patients with carcinoma of the bronchus or lobar pneumonia and patients with allergy to penicillin or cephalosporins were not eligible.

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* This study was coordinated by Dr A. D. Mackay on behalf of a subcommittee of the Research Committee of the British Thoracic Association. Members of the subcommittee were: Dr G. M. Sterling (*Chairman*), Dr I. A. Campbell (*Secretary*), Mr G. Berry (*Statistician*), Dr G. K. Crompton and Dr A. D. Mackay. The report was prepared by Dr A. D. Mackay, whose Research Fellowship was also supported by the Chest, Heart and Stroke Association.

The study was a multi-centre, double-blind, between-patient comparison of:

1. Ampicillin 250 mg orally thrice daily for seven days.
2. Ampicillin 500 mg orally thrice daily for seven days.
3. Amoxycillin 250 mg orally thrice daily for seven days.
4. Amoxycillin 500 mg orally thrice daily for seven days.

The treatments were randomly allocated in balanced blocks of four.

On admission to the trial, details of antibiotic usage in the week prior to entry were recorded, the sputum was graded as purulent or mucopurulent and the oral temperature and pulse rate were noted. Sputum was sent to the local laboratory for microscopy and culture, blood was taken for white blood cell and differential count and a plain posteroanterior chest radiograph was taken.

Treatment consisted of two identical capsules taken three times a day, so that patients on a 250 mg thrice daily regimen received one active and one placebo capsule to make up a dose, whereas those on a 500 mg regimen received two active capsules to make up a dose. Other necessary therapy was given according to the usual practice of the physician.

Following the start of chemotherapy, sputum grading (purulent, mucopurulent, mucoid) was recorded daily by a trained observer on a single fresh specimen taken between 09.00 and 12.00 hours. The temperature was measured four times each day for a week and the peak daily reading recorded. The number and character of bowel motions was noted each day. The patient was examined daily for drug rashes.

At the end of seven days treatment, the physician indicated whether or not he intended to continue antibiotic therapy, and if so for what reason and with what antibiotic. In the case of further treatment the clinical recordings were continued.

Table I. Patient details, clinical findings and investigations at entry

	Ampicillin 250 mg	*Amoxycillin 250 mg*	*Ampicillin 500 mg*	*Amoxycillin 500 mg*
No. of patients	50	42	53	54
Male	41 (82%)	34 (81%)	38 (72%)	41 (76%)
Mean age (years)	66	67	68	65
Antibiotic therapy in the week prior to entry	20 (40%)	19 (45%)	23 (43%)	28 (52%)
Sputum				
Purulent	28 (56%)	22 (52%)	33 (62%)	32 (59%)
Mucopurulent	22 (44%)	20 (48%)	20 (38%)	22 (41%)
Mean pulse rate, min^{-1}	97	92	99	96
Pyrexia	17 (34%)	11 (26%)	21 (40%)	17 (31%)
Radiographic appearances of bronchopneumonia	14 (28%)	13 (31%)	12 (23%)	14 (26%)
Mean total WBC count ($\times 10^9$/litre)	10.5	10.8	10.4	10.4

RESULTS

Patient details, clinical findings and investigations at entry

The comparability of the patients receiving each drug regimen is shown in Table I. The groups were similar in terms of sex, prior antibiotic therapy and the proportions with purulent sputum, pyrexia and radiographic abnormality (χ^2 test). The mean values in the groups for age, pulse rate and total white blood cell count were also similar (unpaired *t*-test). The common pathogens isolated from the sputum were *Haemophilus influenzae* and *Streptococcus pneumoniae*. These pathogens were identified in the sputum of 29% of the patients entering the study.

Failure to complete the week of trial therapy

The numbers of patients who failed to complete the trial therapy are given in Table II together with the reasons for this failure. More deaths occurred on ampicillin regimens than on amoxycillin ones but the overall number of deaths was small and there was no significant difference between the numbers of deaths with each drug (Fisher's exact probability test).

Table II. Failure to complete the week of trial therapy

	Ampicillin 250 *mg*	*Amoxycillin* *250 mg*	*Ampicillin* *500 mg*	*Amoxycillin* *500 mg*
Failure to follow protocol	1	4	2	3
Lack of clinical response	1	1	0	0
Deaths	4	2	3	1
Unwanted effects				
Diarrhoea	1	1	3	0
Skin rash	1	0	2	0
Total	8	8	10	4

Table III. Sputum changes and the need for further antibiotic courses

	Ampicillin *250 mg*	*Amoxycillin* *250 mg*	*Ampicillin* *500 mg*	*Amoxycillin* *500 mg*
No. of patients completing seven days' therapy	42	34	43	50
No. whose sputum became mucoid*	31 (74%)	23 (68%)	30 (70%)	30 (60%)
No. whose sputum still mucopurulent but clinically improved, so no additional therapy given	4	3	9	10
Satisfactory clinical response (no further antibiotics required)	35	26	39	40
% of those entered	70%	62%	74%	74%
% of those receiving week of therapy	83%	76%	91%	80%
No. receiving additional course of antibiotic after trial week	7	8	4	10
* Mean (±SE) No. of days for sputum to become mucoid	5.1±0.29	5.0±0.33	5.2±0.30	5.0±0.27

Clinical progress

Those patients failing to complete the week of trial therapy were excluded from the subsequent analysis of drug efficacy. Table III lists the details of sputum changes and the need for further antibiotic courses. There was no significant difference between the four regimens nor between the two drugs combining the two dose levels, in terms of the number of patients judged to have shown a satisfactory clinical response ($\chi^2=3.13$, 3 DF) or in the mean number of days for the sputum to become mucoid (unpaired t-test).

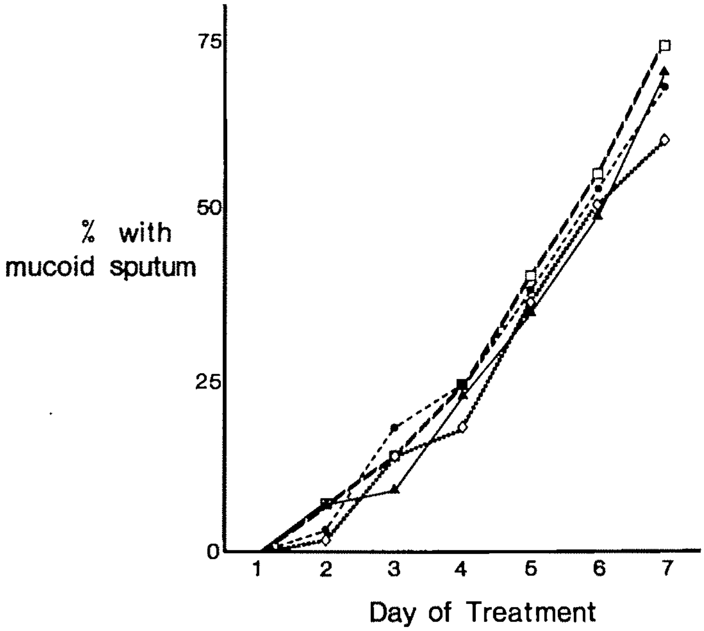

Fig. 1. Cumulative percentage of patients with mucoid sputum on each day of trial therapy for the four regimens. □ — — — □ ampicillin 250 mg; ▲———▲ ampicillin 500 mg; ●--------● amoxycillin 250 mg; and ◇ · · · · · ◇ amoxycillin 500 mg. All regimens were thrice daily

Fig. 1 shows the cumulative number of patients whose sputum had become mucoid on each day of trial therapy for the four regimens, expressed as a percentage of the number who received a week of trial therapy, and illustrates the similar rates of progress on the four regimens. There was no difference in the progress made by those patients who had received antibiotic therapy prior to entry and those who had not.

The response of pyrexia was satisfactory and similar in the four groups.

Unwanted effects

Diarrhoea was infrequent and in only five of 17 patients experiencing an increase in bowel habit did it lead to withdrawal of therapy. One patient withdrew because of diarrhoea on ampicillin 250 mg thrice daily, one on amoxycillin 250 mg thrice daily and three on ampicillin 500 mg thrice daily. There was no significant difference between the two drugs in this respect (Fisher's exact test). Rashes occurred in only four patients, all on ampicillin, three patients being withdrawn because of this: one on ampicillin 250 mg thrice daily and two on ampicillin 500 mg thrice daily. If the combined number of withdrawals for both reasons is considered (Table II) then there is a significant difference between the two high-dose regimens (five withdrawals on ampicillin 500 mg thrice daily as opposed to none on amoxycillin 500 mg thrice daily, $P = 0.03$).

DISCUSSION

May and Ingold (1973) suggested that the clearance of bacteria from the lower respiratory tract would be more easily accomplished with amoxycillin than ampicillin but the few controlled trials comparing amoxycillin and ampicillin have not shown any clinical advantage. A comparative trial in elderly patients with acute respiratory infections showed no difference between amoxycillin and ampicillin in equal dosage of 500 mg thrice daily (Middleton 1974). Anderson et al. (1979) conducted a double-blind comparison of amoxycillin 1.5 g and ampicillin 4 g daily for one week in a group of 25 patients with acute exacerbations of chronic bronchitis and found no significant differences in efficacy and unwanted effects between the treatments.

In the present study of a large group of patients, no significant differences emerged between the four regimens in terms of speed of conversion of the sputum to mucoid or in the number of patients in each group judged to have shown a satisfactory clinical response. Patients were admitted to the trial on clinical grounds and, as might be anticipated, a proportion showed radiographic evidence of bronchopneumonia. No differentiation was made on the basis of radiographic findings as the proportions with shadowing were similar in each treatment group. Unwanted effects were few. Only in a small number of patients did diarrhoea lead to withdrawal of therapy and there was no significant difference between the two drugs in this respect. Drug rashes, although uncommon, were seen only in patients on ampicillin.

The results of this study indicate that the theoretical advantages of amoxycillin are clinically unimportant in the treatment of an acute exacerbation of bronchitis in patients requiring hospital admission. It has been claimed that amoxycillin is more effective than other antibiotics in preventing relapses (Pines et al. 1977) but this aspect has not been examined in the present study and similarly we have no information on the effect of antibiotics on out-patient bronchitics. Although there was a statistically significant difference between the two high-dose regimens in terms of the number of patients withdrawing because of adverse effects, the clinical importance of this difference is probably slight as there would appear to be no particular advantage in using the high rather than the low dose. The decision as to which antibiotic to prescribe can be based purely on availability and relative cost.

Without a placebo group the satisfactory clinical progress seen in the present patients cannot definitely be attributed to chemotherapy, and one interpretation of the similarity in response to high- and low-dose regimens is that the antibiotic played only a minor role. The value of antibiotic therapy in the hospital treatment of exacerbations of chronic bronchitis has been questioned previously. Elmes et al. (1965) found no advantage of ampicillin over placebo in a double-blind trial, although Pines et al. (1972), using tetracycline or chloramphenicol, did show temporary benefit over a placebo. In view of these conflicting results and the present findings, further studies are required to establish the role of broad-spectrum antibiotics in the management of patients admitted to hospital with acute exacerbations of chronic bronchitis.

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AMINOPHYLLINE, SALBUTAMOL AND COMBINED INTRAVENOUS INFUSIONS IN ACUTE SEVERE ASTHMA

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Summary

Twenty-one patients admitted to hospital with acute severe asthma were allocated in a random, single-blind manner to receive intravenous infusions for 24 hours of either aminophylline or salbutamol or a combination of the two drugs.

Infusions were administered by a slow infusion pump with an initial loading dose given over 15 minutes, followed by a continuous lower dose of the drug for 24 hours as follows:

1. Aminophylline 0.285 mg/kg/min for 15 min followed by 0.014 mg/kg/min (20 mg/min. followed by 1 mg/min for a 70 kg subject).
2. Salbutamol 0.285 μg/kg/min for 15 min followed by 0.057 μg/kg/min (20 μg/min followed by 4 μgm/min for a 70 kg subject).
3. Combined regimen of the above infusions.

In addition each patient received intravenous hydrocortisone (4 g) and potassium chloride (4 g) in 2 litres of 5% dextrose infused over 24 hours and 35% oxygen given via a Ventimask.

Peak expiratory flow rates showed a significant improvement after 15 minutes treatment with aminophylline and the combined infusion, but this was not seen until 60 minutes with the salbutamol infusion. No synergistic bronchodilator effect was seen with the combined infusion. The results show that intravenous aminophylline is superior to intravenous salbutamol in the doses given in the initial treatment of acute asthma and that the combination when given intravenously is not better than aminophylline alone.

INTRODUCTION

Bronchodilators and corticosteroids are used routinely in the treatment of acute asthma. Two effective bronchodilators are aminophylline, a phosphodiesterase inhibitor, and salbutamol, a selective β_2 adrenoceptor agonist. Because these drugs act at different sites in the metabolic pathway of cyclic AMP, when used together they might be expected to act additively or even synergistically. Such interaction has in fact been demonstrated in the laboratory (Kaliner et al. 1971) and in stable asthmatics (Campbell et al. 1977). This study was designed to show whether such a beneficial interaction occurred between intravenous aminophylline and intravenous salbutamol in acute severe asthma.

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Patients and Methods

Twenty-one patients with acute asthma who gave informed consent were included in the study. All had pulse rates greater than 120/min, PEFR less than 25% predicted (Cotes 1975) and arterial oxygen tensions less than 9.3 kPa (70 mmHg). Patients less than 15 years of age and those who had received parenteral bronchodilator therapy less than three hours prior to admission were excluded from the study.

Each patient was randomly allocated to one of the infusion regimens, administered by a slow infusion pump (Palmer). All the infusions consisted of an initial loading dose given over 15 minutes followed by a continuous lower dose of the drug for the following 24 hours.

Dosages were as follows:

1. Aminophylline 0.285 mg/kg/min for 15 minutes followed by 0.014 mg/kg/min for 24 hours (20 mg/min and 1 mg/min respectively for a 70 kg person).
2. Salbutamol 0.285 μg/kg/min for 15 minutes followed by 0.057 μg/kg/min for 24 hours (20 μg/min and 4 μg/min respectively for a 70 kg person).
3. Combined regimen of (1) and (2) administered via double outlet infusion pump, avoiding extracorporeal mixing.

In addition, each patient received intravenous hydrocortisone (4 g) and potassium chloride (4 g) in 2 litres of 5% dextrose infused over 24 hours. 35% oxygen was given via a Ventimask, but inhaled bronchodilators were withheld for the period of the infusion. Measurements of the pulse rate, blood pressure and PEFR were made before treatment was started, and progress was monitored by repeating these measurements at 15-minute intervals for the first hour and then at six-hourly intervals for the following 24 hours. Arterial blood gases were measured before treatment and one, 12 and 24 hours after the start of treatment. Electrocardiographs were recorded as soon as possible after admission. Results were analysed as the mean peak increase or decrease during drug infusion, both as absolute values and percentage change. Significance values were obtained using Student's *t*-test for unpaired and paired samples, as appropriate.

Table I. Sex, age and pulmonary and cardiovascular function (mean ± SE) measured before treatment

Group	*No.*	*Sex*	*Age* (years)	*PEFR* (litres/min)	*Pulse rate* (/min)	Pa_{O_2} (kPa)	Pa_{CO_2} (kPa)
Aminophylline infusion (A)	6	4M, 2F	22 ± 5	105 ± 40	131 ± 9	7.4 ± 1.3	5.8 ± 0.9
Salbutamol infusion (S)	7	3M, 4F	33 ± 16	89 ± 45	123 ± 2	7.5 ± 1.5	5.2 ± 1.4
Combined infusion (C)	8	2M, 6F	28 ± 10	78 ± 23	123 ± 2	7.3 ± 0.7	4.6 ± 0.7
t-tests A/S				NS	NS	NS	NS
C/S				NS	NS	NS	NS
A/C				NS	NS	NS	$P = 0.02$

RESULTS

Twenty-one patients were studied (Table I), six of whom (four male) received aminophylline, seven (three male) salbutamol and eight (two male) the combined infusion. All groups were similar with respect to age, weight, PEFR, pulse rate and Pa_{O_2} at the start, although Pa_{CO_2} was significantly higher in the aminophylline group than the combined group.

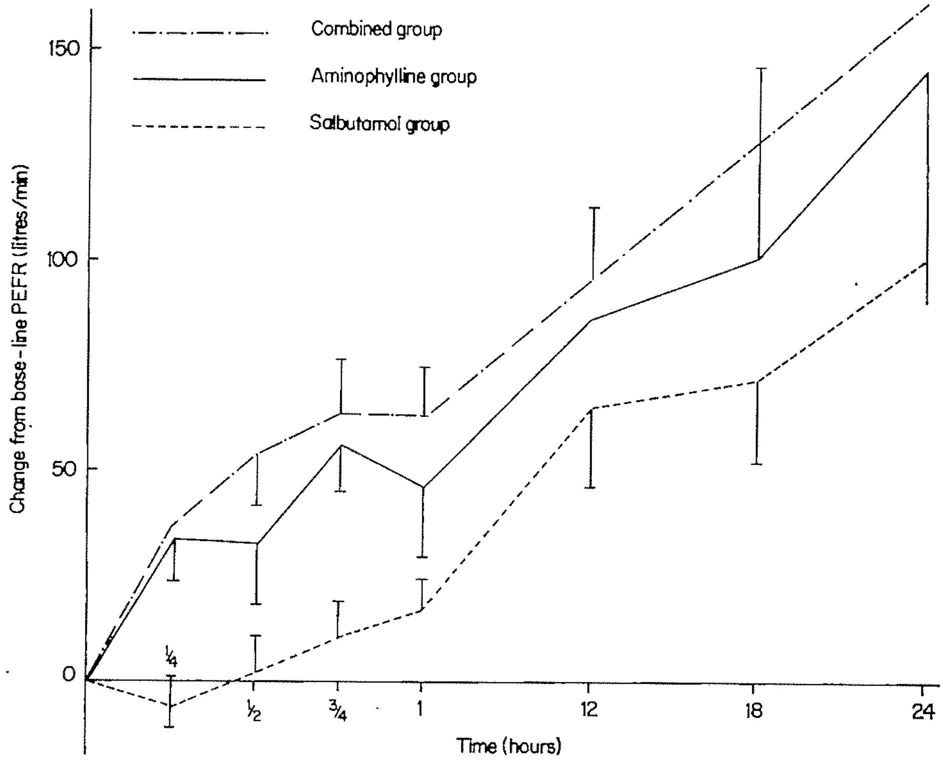

Fig. 1. Absolute change (±SE) in mean peak expiratory flow rate after start of infusions in the three groups

Table II. Time taken for PEFR to improve in the three groups (mean ± SE)

Group	*Time to 50% max. PEFR* (hours)	*Time to max. PEFR* (days)	*Convalescent PEFR*
Salbutamol infusion (S)	29 ± 16	9 ± 5	428 ± 143
Aminophylline infusion (A)	24 ± 12	7 ± 2	463 ± 117
Combined infusion (C)	21 ± 13	9 ± 3	425 ± 55
t-tests A/S	NS	NS	NS
C/S	NS	NS	NS
A/C	NS	NS	NS

Significant bronchodilatation was seen within 15 minutes in the combined and aminophylline treatment groups, but not until 60 minutes in the salbutamol group (Fig. 1). There was no significant difference in the time taken for patients to achieve 50% maximum PEFR (Table II). Mean pulse rates fell with aminophylline, remained the same with salbutamol and increased in the combined infusion group (Fig. 2). Changes in the arterial gases were the same for each group. ECG changes were similar in the three groups; all had a sinus tachycardia, 11 had p pulmonale, one had right bundle-branch block and one had acute right ventricular strain pattern. These changes were transient and returned to normal on recovery from the asthma.

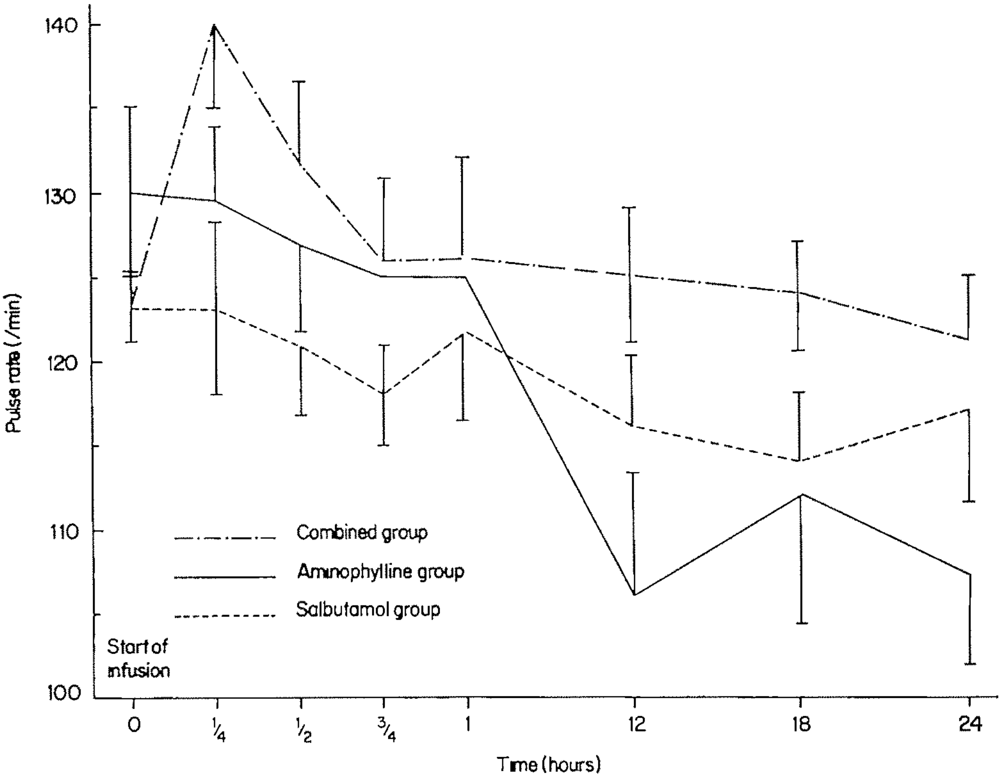

Fig. 2. Mean pulse rates (±SE) after start of infusions in the three groups

DISCUSSION

The dose of intravenous aminophylline in the treatment of acute asthma is well evaluated (Nicholson & Chick 1973; Mitenko & Ogilvie 1973). The same does not apply to salbutamol. Smith (1974) found cardiovascular side-effects at infusion rates in excess of 20 μg/min, and in acute asthma this dose produced an unacceptable incidence of side-effects (Lawford et al. 1978). In convalescent asthmatics receiving continuous infusions of salbutamol the major bronchodilator effect was seen at 4 μg/min with little further improvement at higher infusion rates (May et al. 1975). Although infusion rates of 10 μg/min have been given safely in acute asthma (Johnson et al. 1978), for the continuous infusion in this study we chose the lower dose to avoid the possibility of increased cardiovascular side-effects when combined with aminophylline. Cumulative bolus dose studies of salbutamol showed optimal bronchodilatation after 300 μg (Spiro et al. 1975), but because this produced marked tachycardia when administered rapidly we infused this same dose over a 15 minute period.

The results show no significant synergistic or additive bronchodilator effect when a combination of intravenous aminophylline and salbutamol were used at the above dosages, and thus we were unable to confirm the previous findings in stable asthmatics (Campbell et al. 1977). Although the combined regimen appeared to produce more bronchodilatation than aminophylline alone, the patients receiving aminophylline had more severe asthma with a higher base-line $P\text{a}CO_2$. A significant tachycardia was produced in the combined infusion group, compared with the salbutamol group, but no other serious side-effects were seen in the patients studied.

The bronchodilator response was significantly better ($P < 0.005$) in the aminophylline group when compared with the salbutamol group at 15 minutes. Salbutamol had very little effect for the first 45 minutes in spite of the high loading dose of 20 μg/min of the drug for 15 minutes. This confirms the finding of Johnson et al. (1978) that significant bronchodilatation took longer to occur with salbutamol than with aminophylline infusions in acute asthma. These results conflict with those of Williams et al. (1975) who found short infusions of salbutamol as effective as aminophylline. In that study loading doses of drug were not used and salbutamol and aminophylline were infused at rates of 8 μg/min and 9 mg/min respectively, compared with 20 μg/min and 20 mg/min used initially in this study. Thus the dose of aminophylline used in the previous study was probably sub-optimal (Maselli et al. 1970; *Lancet* 1973) and the higher dose used in the present study is to be preferred.

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PREOPERATIVE CARCINOEMBRYONIC ANTIGEN AND SURVIVAL AFTER RESECTION OF LUNG CANCER

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Summary

Carcinoembryonic antigen (CEA) was measured preoperatively in 43 patients who underwent complete resection of primary lung cancer. 7 of 43 patients (17%) had CEA levels in the cancer diagnostic range (>40.9 μg/litre), none of whom survived longer than 10 months. At two years, it was apparent that those patients with a preoperative CEA less than 21 μg had a better survival rate than those with a CEA 21–40.9 μg/litre ($P < 0.005$).

INTRODUCTION

Raised levels of CEA have been detected in the plasma of patients with non-gastrointestinal malignancies, including lung cancer (Lo Gerfo et al. 1971; Vincent & Chu 1973). Laurence et al. (1972) established that a normal control population between the ages of 30 and 40 years had a plasma CEA content of less than 15 μg/litre. Hansen et al. (1974) have shown that the level may be raised by smoking and non-specific factors into the range of 14–40 μg/litre. These non-specific factors are unlikely to cause levels in excess of 40 μg/litre and levels above this should be regarded as evidence of CEA-producing tumours (Mackay et al. 1974). In a large group of patients with lung cancer, Vincent et al. (1975) showed that an elevated CEA indicated a poor prognosis.

The present study was designed to assess whether pre-operative CEA measurements were of any value in predicting the survival of patients with lung cancer following complete resection of primary tumour.

Materials and Methods

43 patients with lung cancer who underwent complete resection of the primary tumour were studied. Preoperative staging of the disease included mediastinoscopy, bronchoscopy, biochemical tests of liver and bone function and liver and bone scans. Plasma samples were drawn on two occasions prior to surgery and stored at −20°C for later testing by the radio-immunoassay technique described by Laurence et al. (1972). In this study the upper limit of normal for CEA was set at 20.9 μg/litre. Patients were divided into three groups according to the preoperative CEA result: those with a CEA in the normal range 0–20.9 μg/litre, those showing a 'non-specific' rise in CEA to 21–40.9 μg/litre and those with a CEA in the cancer diagnostic range. Patients were seen at six- to eight-week intervals following surgery and serial CEA measurements were made during the first year. Survival was analysed by χ^2 test at one and two years and survival trend using the χ^2 test for trends in proportions.

RESULTS

Preoperative CEA levels and survival according to cell type of tumour are shown in Table I. All seven patients with a preoperative CEA greater than 40.9 μg/litre had died by the end of one year compared to 13 of 36 with a CEA less than this ($P < 0.02$). There was no difference in survival at one year between those patients with a preoperative CEA in the normal range and those with CEA 21–40.9 μg/litre. Two years after operation a trend of survival was apparent where 57% of patients with CEA in the normal range, 31% of patients with CEA in the range 21–40.9 μg/litre and none of patients with CEA greater than 41 μg/litre were surviving ($P < 0.005$).

Serial measurements were made and these are illustrated for two groups of patients. Fig. 1 shows CEA before and at 10–12 months after excision of the tumour for 21 of 23 patients who survived one year. A slight fall occurred in most cases after the operation. CEA had risen to greater than 40.9 μg/litre in two patients, both of whom subsequently developed liver and bone metastases. When CEA was greater than 40.9 μg/litre preoperatively (Fig. 2) an initial fall in CEA sometimes occurred, but for most patients the levels continued to rise, and mean survival for seven patients shown in Fig. 2 was three and a half months. Two patients with CEA levels of 500 μg/litre died within a few weeks of operation from rapidly progressive metastatic disease. However, another 13 patients died in the first year after resection, of whom nine had a preoperative CEA in the normal range and four in the range 21–40.9 μg/litre. Serial CEA measurements did not bear any relationship to disease progression.

Table I. Preoperative CEA level related to histological cell type and length of survival

CEA level	*Squamous carcinoma*	*Adenocarcinoma*	*Small cell and anaplastic*	*Total*
0–20.9 μg/litre				
No. of patients	15	6	2	23
Alive at one year	11	2	1	14 (61%)
Alive at two years	10	2	1	13 (57%)
21–40.9 μg/litre				
No. of patients	8	2	3	13
Alive at one year	8	1	0	9 (69%)
Alive at two years	4	0	0	4 (31%)
41+ μg/litre				
No. of patients	5	2	0	7
Alive at one year	0	0	0	0

There was no correlation between the size of the tumour or local lymph node involvement of the resected specimen and the preoperative CEA level. The most favourable prognosis occurred in patients with squamous cell cancer who had a preoperative CEA in the normal range.

DISCUSSION

In this series, all patients with a preoperative CEA in excess of 40.9 μg/litre developed recurrence of metastases within three and a half months of apparent curative resection.

The findings are in agreement with those of Vincent et al. (1975, 1978). However, 13 of 36 patients with a preoperative CEA less than 40.9 μg/litre also died in the first year after surgery and in these the preoperative CEA did not bear any relationship to subsequent events.

The observation that the trend of survival diminished with higher preoperative CEA levels has also been reported by Concannon et al. (1978). CEA rose in excess of 41 μg/litre before the end of the first postoperative year in two of six patients who developed metastases between 12 and 24 months and in these cases it could be used to monitor disease progression. The four remaining patients who died in the second year had had preoperative CEA levels in the range 21–40.9 μg/litre and changes in CEA were not observed throughout the follow-up period. In these cases it is possible that these were non-specific rises and merely either indicated general debility with diminished resistance to tumour spread, or were due to other lung disease, such as chronic bronchitis or emphysema (Hansen et al. 1974).

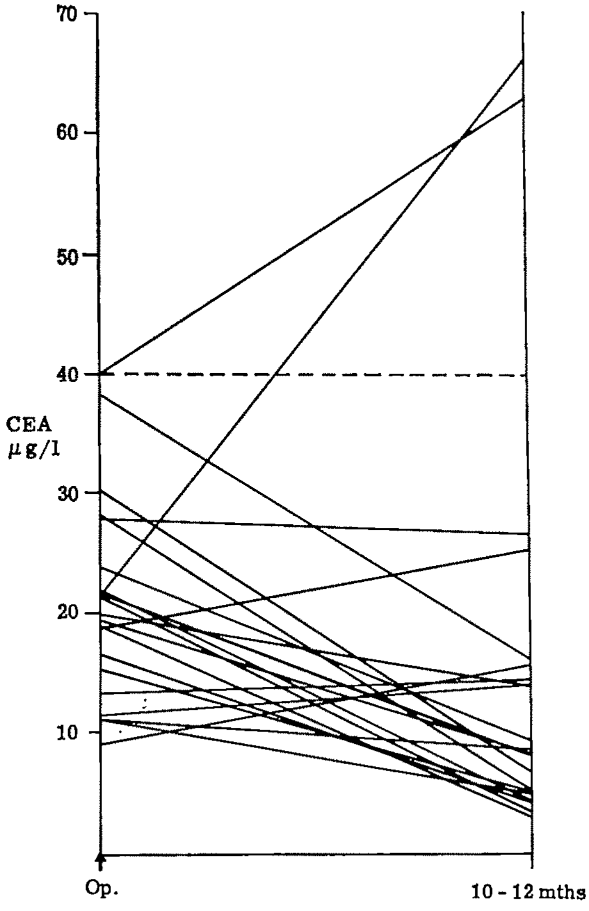

Fig. 1. Preoperative CEA levels and levels 10–12 months after tumour resection in 21 of the 23 patients who survived for more than one year

Only 15–20% of lung cancers are associated with preoperative CEA levels in the cancer diagnostic range, and in these cases it can be used as a marker for recurrent disease following treatment (Ford et al. 1977). However, the data of Vincent et al. (1978) and Concannon et al. (1978), together with the evidence presented here, would indicate that those lung cancers associated with a preoperative CEA of 41 μg/litre or greater have already metastasized and that surgery alone as the only form of treatment is unlikely to benefit the patient. A lower preoperative CEA is associated with an improved two-year survival following tumour resection and if the level falls within the normal range, 50% of these patients are alive two years later.

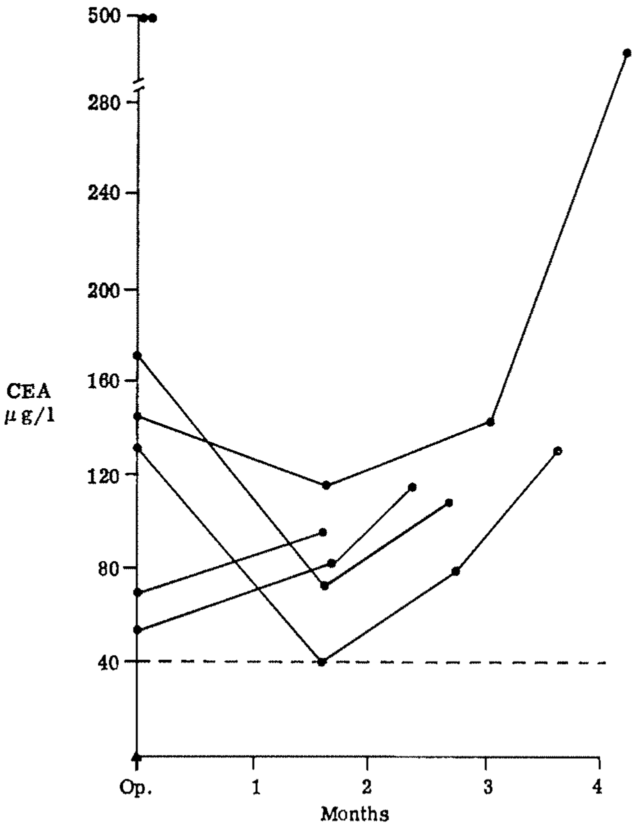

Fig. 2. Serial CEA levels in five of the patients who had a preoperative CEA >40 μg/litre

We suggest that routine measurement of CEA before surgery would identify a small group of patients who are likely to have metastatic disease and thorough investigation is necessary before surgery is undertaken. Patients with non-specific rises of CEA in the range 21–40 μg/litre before surgery fare worse two years after operation than those who have a CEA in the normal range. When the preoperative CEA is less than 40.9 μg/litre, recurrence of disease is only rarely associated with rises greater than this level into the cancer diagnostic range, thus limiting the usefulness of CEA in monitoring the disease process.

ACKNOWLEDGEMENTS

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Br. J. Dis. Chest (1980) *74*, 395

TRAINING AID FOR PRESSURIZED INHALERS

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Drugs administered by pressurized inhalers play a major role in the treatment of bronchial asthma. The use of pressurized inhalers demands an adequate tidal volume and accurate synchronization of the discharge of the aerosol with the phase of respiration (Paterson 1978). Estimates of the proportion of patients who fail to use pressurized inhalers efficiently vary between 14% (Paterson & Crompton 1976) and 75% (Orehek et al. 1976). This proportion is dependent upon the amount of training received and increases when there are difficulties of communication between doctor and patient. Failure to synchronize inhaler discharge with the commencement of inspiration is a major source of inefficiency (Orehek et al. 1976). A simple training aid has been devised to overcome this problem in a multiracial group of asthmatics in Borneo.

Method

The training aid consists of a thermistor mounted in the mouthpiece of a placebo pressurized inhaler connected via a simple electronic circuit and a 9 V battery to a light-emitting diode (LED) situated at the top of the inhaler, and clearly visible to the patient (Fig. 1). Cold air being drawn over the thermistor at the onset of inspiration causes a fall in resistance which is corrected to a rapid switching effect by the electronic circuit. This activates the LED which remains lit whilst the temperature continues falling until the end of inspiration.

Patients wearing a nose-clip were instructed to insert the mouthpiece of the inhaler into the mouth and breathe in and out through the inhaler slowly and deeply, whilst observing the light on the inhaler going on and off with inspiration and expiration. When this was being performed correctly, the patient was instructed to discharge the inhaler when they saw the light come on, continue to breathe in deeply and then hold their breath. After an initial training session, the patients were loaned a teaching inhaler for one week, after which they were reassessed.

RESULTS

The teaching aid is self-compensating for changes in ambient temperature and in practice operated reliably provided the ambient temperature was less than 32°C, the LED coming on instantaneously at the onset of inspiration. In the Brunei Asthma Clinic, all patients undergo intensive initial tuition in inhaler technique and this is checked at each visit. However, of 40 Brunei asthmatics (26 Malay, 12 Chinese, 2 Iban) seen consecutively at follow-up, 12 (30%) were assessed as being inefficient in using their pressurized inhalers due to poor synchronization of inspiration with aerosol discharge and subsequently underwent tuition with the training inhaler. Despite language difficulties (six different dialects), all the patients quickly understood the visible signal to discharge the inhaler and, when reassessed after one week, 10 of the 12 patients (83%) were reclassified as efficient in the use of pressurized inhalers.

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DISCUSSION

Drugs delivered by pressurized inhalers now form the basis of the maintenance treatment of asthma. Despite careful initial tuition and regular checking of technique, many asthmatics are unable to use their inhalers efficiently due to poor synchronization of aerosol discharge with the commencement of inspiration. The author has discovered that this problem is greater in a multiracial community with many different dialects, when it is very difficult to explain the finer details of inhaler usage to patients. A training aid

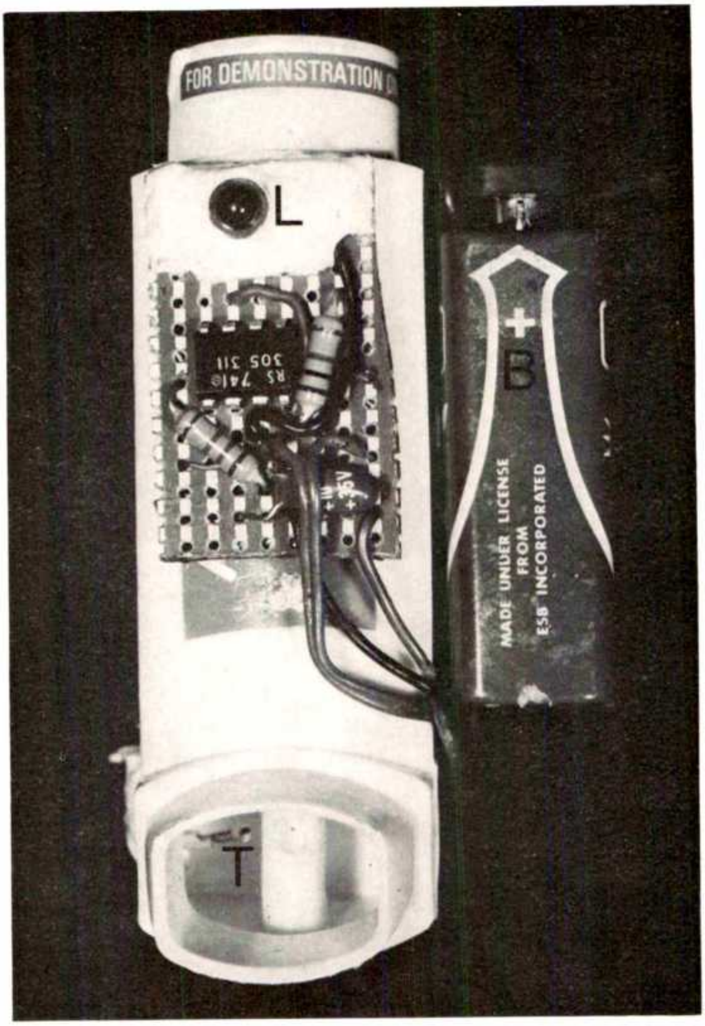

Fig. 1. The training inhaler. B = battery; L = light emitting-diode; T = thermistor.

which provides a visual signal at the onset of inspiration has helped to overcome this problem. The device is small in size, simple in design and operation, and self-compensating for changes in ambient temperature. Whilst it has a particularly useful role when there are difficulties in doctor–patient communication, it may be useful in retraining difficult patients and in teaching children. Its cheapness (less than £2.00 for components) and reliability make domiciliary use feasible and it will be possible to incorporate the device within the plastic case of an inhaler.

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A CONTROLLED TRIAL OF KETOTIFEN IN EXERCISE-INDUCED ASTHMA

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Summary

We studied 17 patients in a double-blind controlled trial to see if ketotifen, a new oral mast-cell stabilizing agent, would protect against bronchoconstriction induced by exercise on a treadmill. In addition eight of the patients also completed exercise tests without previous medication and again after inhalation of disodium cromoglycate (DSCG). The greatest amount of bronchoconstriction was caused by exercise without preliminary treatment. There was less bronchoconstriction after ketotifen, but this was no better than a placebo. DSCG provided significant protection. We were unable to confirm previous reports that ketotifen is as effective as DSCG in preventing exercise-induced asthma.

INTRODUCTION

Wheezing provoked by exertion is a troublesome feature in many asthmatic patients and may occasionally be the main manifestation of asthma. Davies (1968) and Blackhall and Jones (1970) showed that preliminary treatment with DSCG would inhibit exercise-induced wheezing in some, but not all, asthmatics and this has since been confirmed in many laboratories. DSCG is thought to act as a mast-cell stabilizer (Cox & Altounyan 1970). Ketotifen is a new oral agent with similar mast-cell stabilizing effects (Martin & Roemer 1977). We therefore performed a double-blind controlled trial to measure the effects of ketotifen on bronchoconstriction induced by exercise on a treadmill and to compare the results with those in untreated patients and those treated with DSCG and placebo.

Patients and Methods

Seventeen patients with a clear history of asthma provoked by exertion gave informed consent to the studies. There were 12 men and five women with an average age of 30 years (range 14–60). All performed a standard exercise test which consisted of walking on a treadmill at an incline of 10% for six minutes at 5 km/hour. Peak flow rates (PFR) were measured with a Wright peak flow meter. Forced vital capacity (FVC) and forced expiratory volume in one second (FEV_1) were measured with a dry spirometer (Vitalograph). PFR, FVC and FEV_1 were recorded immediately before the six-minute period of exercise, immediately after exercise (except, inadvertently in one patient, see Fig. 1), and at five-minute intervals for 20 minutes. The best of three attempts was recorded. Nine patients performed the exercise test without preliminary medication and at least 12 hours after bronchodilator therapy. After at least one week the exercise test was repeated five minutes after the inhalation of 20 mg DSCG. These patients and eight others, a total of 17 patients, then took part in a double-blind cross over trial with ketotifen and placebo. Each received one capsule of either 1 mg of ketotifen or an apparently similar placebo capsule twice daily for three days, with a seventh capsule given four hours before the exercise test. The active and placebo capsules were given in accordance with a previously prepared random schedule and the nature of the capsules was not determined until the conclusion of the trial. Each patient completed two exercise tests in the double-blind part of the trial, receiving both active and placebo capsules as described. The dose used had previously been shown (Craps et al. 1978) to be effective in preventing exercise-induced asthma.

Patients who were wheezy after their exercise tests were treated with bronchodilators as appropriate.

Table I. Mean peak flow rate before exercise

No.	*PEFR before exercise* (litres/sec)			
	No drug	DSCG	Ketotifen	Placebo
9	6.58	6.88	6.88	6.56
8			6.98	6.66
All (17)			6.93	6.61

Table II. Greatest percentage fall in peak expiratory flow rate after exercise

Patient	*Fall in PEFR* (%)			
	No drug	DSCG	Ketotifen	Placebo
1			34	12
2			3	14
3			28	0
4			32	42
5			0	5
6			8	13
7			18	7
8			17	11
9	10	8	8	2
10	52	20	57	41
11	28	6	14	21
12	17	0	0	3
13	24	1	10	5
14	26	0	17	18
15	20	24	7	10
16	59	0	59	47
17	14	0	0	2
Mean (9–17)	27.8	6.5	19.1	16.6
Mean (1–17)			18.4	14.9

RESULTS

The exercise tests caused similar changes in PFR, FVC and FEV_1, so only the PFR results are quoted. There was little difference in the PFR values at the start of each phase of the trial, and the mean values are given in Table I. In the double-blind trial, completed by 17 patients, there were no significant differences between the changes after exercise whether the patients had taken ketotifen or a placebo (*t*-test, $P > 0.5$). The mean of the greatest percentage fall in peak flow rate was 18.4 after ketotifen and 14.9 after placebo (Table II). In the nine patients who each completed four exercise tests the mean of the greatest percentage fall in PFR was 27.8 with no treatment, 19.1 after ketotifen, 16.6 after placebo and 6.5 after DSCG (Table II). The results of the exercise tests are illustrated in Fig. 1. The patients were significantly less wheezy when exercising after DSCG than without treatment ($P < 0.01$), but ketotifen ($P > 0.3$) and placebo ($P > 0.3$) did not produce any statistically significant improvement.

No side effects from ketotifen were recorded.

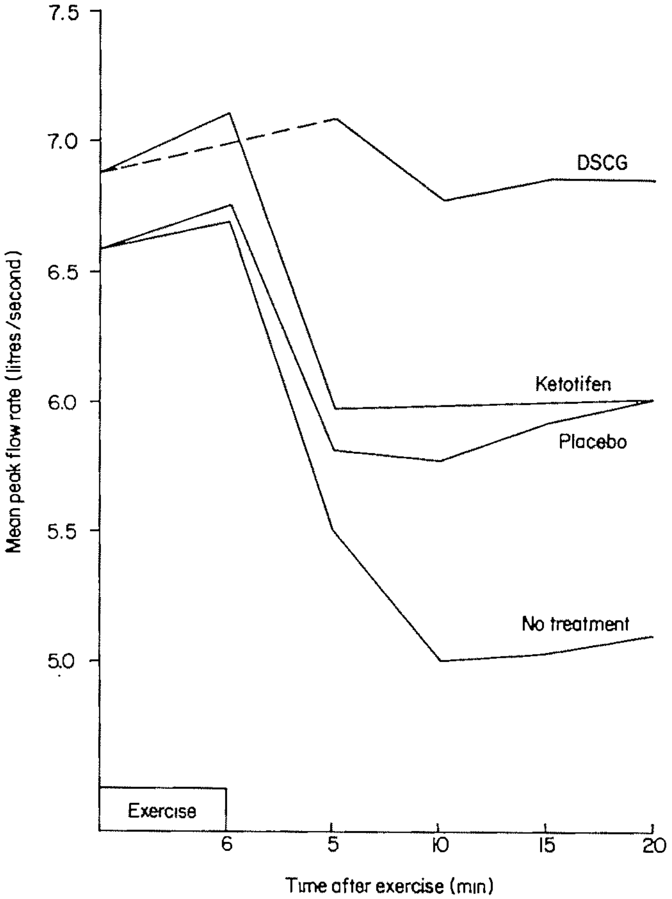

Fig. 1. The change in mean peak flow rates produced by exercise in nine patients

DISCUSSION

The role of ketotifen in the management of asthma has not yet been established. It has been shown to have mast-cell stabilizing effects (Martin & Roemer 1977) and early clinical studies suggested that ketotifen was as effective as cromoglycate in protecting against antigen challenge (Craps et al. 1978; Debelic et al. 1976; Girard & Cuevas 1977; Pauwels et al. 1978; Wuethrich et al. 1978). The later study of Wells and Taylor (1979) failed to confirm this effect. Craps et al. (1978) and Wuethrich et al. (1978) also showed that ketotifen was as effective as DSCG in preventing exercise-induced asthma. In both these studies, the exercise was performed on a bicycle ergometer and this has been shown to produce less fall in PFR than a treadmill (Anderson et al. 1972). In neither of the ketotifen studies was a placebo used, although the work of Godfrey et al. (1973) has shown that placebo injections or inhalations appear to reduce the bronchoconstrictor effect of exercise in children. This study confirmed a small placebo effect, this time with oral medication, but did not demonstrate any difference between ketotifen and a placebo when used in a double-blind trial. The protective effect of DSCG was confirmed, although it was not effective in all patients.

Ketotifen appears to have inconsistent effects in laboratory studies. It has also been shown to have inconsistent effects in more prolonged therapeutic trials. Craps et al. (1978) judged ketotifen to be 'very effective' or 'effective' in 45 of 55 patients in a dose of 1 mg twice daily. Weheba (1978) found a significant reduction in the incidence and duration of asthmatic attacks with the same dose of ketotifen in 33 or 35 adult patients. This beneficial effect was not found in a later three week trial in 20 asthmatic children (Taylor & Ford 1979), although a recent multi-centre double-blind investigation demonstrated a steroid sparing effect when ketotifen was given to asthmatics (Lane 1980). This suggests that ketotifen does not act in a similar way to DSCG although it does appear to stabilize mast cells in vitro. The place of ketotifen in the management of chronic asthma remains to be determined.

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Short Communication

IS INDORAMIN USEFUL IN THE TREATMENT OF BRONCHIAL ASTHMA?

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A previous study by the British Thoracic Association (Campbell & Dyson 1977) showed that indoramin, an orally active alpha-adrenoreceptor antagonist, produced a small increase in peak flow rate in a mixed group of patients with airways narrowing. Utting (1979), however, was unable to show benefit in severe asthma. We have performed a double-blind trial of indoramin in patients with mild asthma.

Patients and Methods

Patients eligible were aged 18–65. Their forced expiratory volume in one second (FEV_1) was between 40 and 70% predicted normal and increased by at least 20% after inhalation of 160 μg isoprenaline. Patients taking any other medication, except inhaled salbutamol or oral contraceptives, were excluded.

Each patient was taught to use a peak flow gauge twice daily and to record the results together with the number and timing of doses of inhaled salbutamol used for relief of symptoms. Patients recorded the severity of breathlessness, quality of sleep and degree of daytime alertness by marking three lines daily. Patients were seen weekly and questioned about exercise tolerance, number of attacks of breathlessness by night and day, additional treatment and the presence of unwanted effects. Blood pressure, weight and any oedema were recorded and FEV_1 and vital capacity were measured before and after inhaling isoprenaline. At the first and final visit blood was taken for haematological and biochemical measurements and urine was tested for glucose and protein.

For the first week each patient received two placebo tablets thrice daily to become familiar with recording techniques and then, during four two-week treatment periods, received in random order 0, 30, 60 or 90 mg of indoramin daily in three doses each of two white tablets.

RESULTS

Twenty-two patients, 15 male, mean age 42, entered the study. Four centres enrolled 12, six, three and one patients respectively. Two withdrew during the first treatment period at a daily dose of 0 mg. Two female patients withdrew because of shakiness and palpitations, one while receiving 90 mg daily, the other during the second treatment period after reduction from 60 mg to 0 mg daily. One patient developed a chest infection during the second week. A sixth patient failed to attend after seven weeks. Sixteen patients remained.

Mean values of measurements recorded during the second week of each treatment period are shown in Table I. Those for peak flow rate excluded measurements made within four hours after inhalation of salbutamol. There were no statistically significant differences. Scores for exercise tolerance and for attacks of diurnal or nocturnal breathlessness showed no change in relation to any treatment period.

One patient who had previously received diuretic therapy developed oedema. Thirteen patients described side-effects. All commenced during periods of active treatment and in

Table I. Mean values (± SD) for measurements during each period of indoramin treatment

	Dose of indoramin (mg/day)			
	0	30	60	90
Diary card				
Peak flow (litres/min)	357 ± 111	357 ± 100	371 ± 90	365 ± 82
Salbutamol (puffs/week)	32 ± 30	32 ± 33	34 ± 49	31 ± 32
Breath score	210 ± 74	215 ± 47	212 ± 72	209 ± 53
Sleep score	220 ± 75	221 ± 59	223 ± 88	215 ± 60
Alertness score	216 ± 49	201 ± 49	203 ± 66	192 ± 52
Clinical measurements				
FEV_1 before isoprenaline (litres)	2.28 ± 1.04	2.32 ± 1.02	2.20 ± 0.91	2.27 ± 1.01
FEV_1 after isoprenaline (litres)	2.51 ± 1.13	2.64 ± 1.13	2.54 ± 1.07	2.48 ± 1.12
Systolic blood pressure (mmHg)	128 ± 18	127 ± 17	123 ± 18	122 ± 19
Diastolic blood pressure (mmHg)	80 ± 16	78 ± 14	78 ± 17	76 ± 10

seven patients occurred only with the 90 mg dose. Four patients reported drowsiness, two dizziness and one loss of consciousness. He showed postural hypotension (supine blood pressure 160/100, erect 100/60) when taking 90 mg indoramin. Three patients had headache, three dry throats and blocked noses, one a transient morbilliform rash and one failure of ejaculation. There were no important haematological or biochemical changes.

DISCUSSION

The previous study by Campbell and Dyson (1977) suggested a small but not clinically useful effect of indoramin in a mixed group which included patients with chronic bronchitis and emphysema and some taking corticosteroids and cromoglycate. All received regular inhaled salbutamol. Neither that study nor the present one showed any evidence that indoramin improved the response to inhaled isoprenaline. Utting (1979) found no benefit in 39 patients with asthma which was severe enough to require corticosteroids. We have studied patients whose asthma was mild and, like Utting, have been unable to show any significant improvement while taking 90 mg of indoramin daily for two weeks. The incidence of side-effects was very high.

Symptoms may have been elicited more easily from patients because of the inclusion of a direct question in the weekly questionnaire, but all were related to active treatment and were most common during the periods of highest dosage.

This study shows no place for indoramin in the treatment of mild bronchial asthma.

ACKNOWLEDGEMENTS

This study was initiated by the Clinical Trials Subcommittee of the British Thoracic Association. We should like to thank John Wyeth and Brother Limited for financial support, Dr P. Southgate and Dr E. Makin for their cooperation and Mrs C. Brown and Mrs D. Kingham for assistance.

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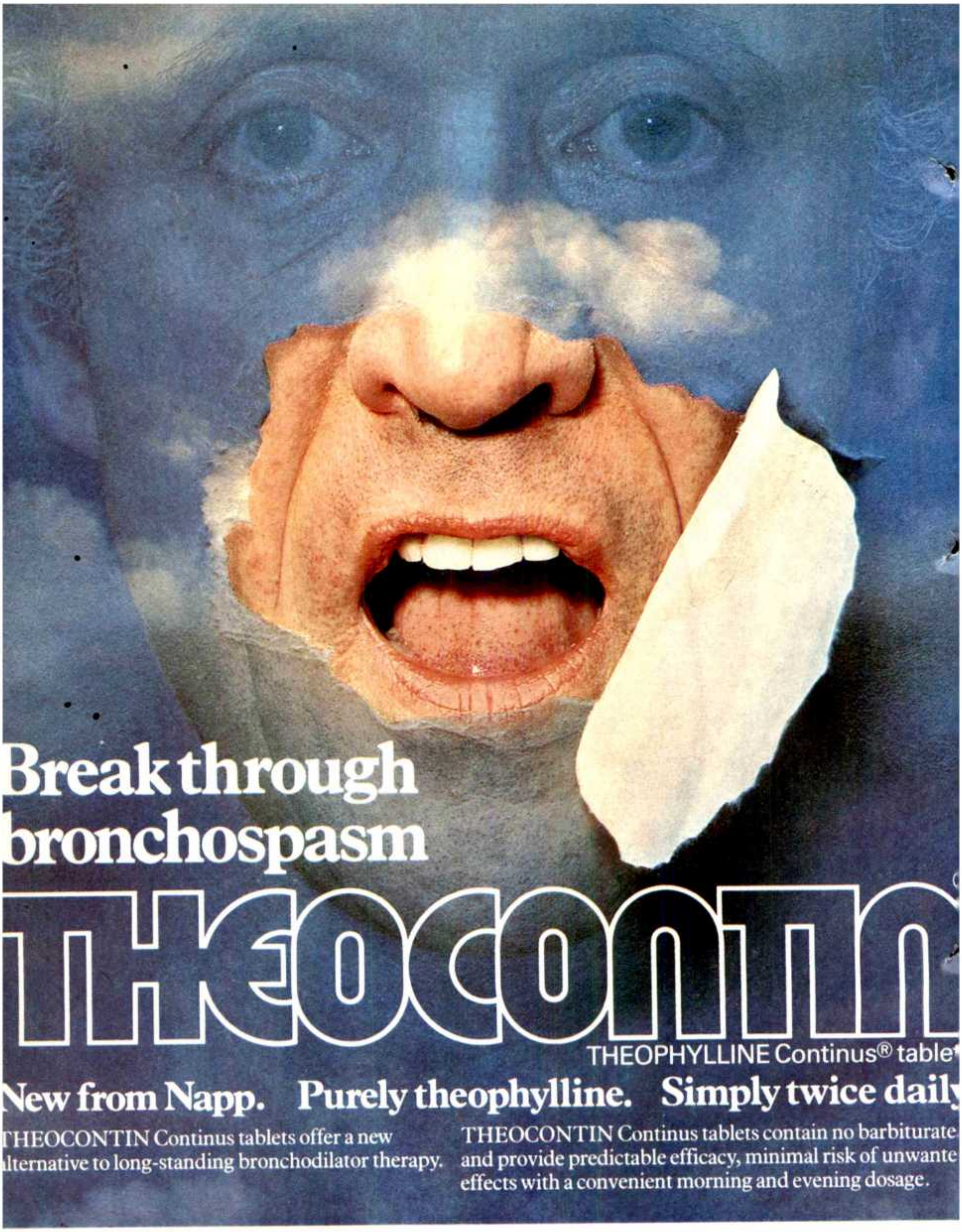

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RIFAMPICIN-INDUCED PORPHYRIA CUTANEA TARDA

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Summary

A patient who developed porphyria cutanea tarda and disturbed liver function tests following treatment with rifampicin and isoniazid for a tuberculous psoas abscess is reported. The patient had normal liver function tests prior to receiving anti-tuberculosis chemotherapy, but was subsequently demonstrated to have cholelithiasis. Challenge testing with both drugs incriminated rifampicin as the agent precipitating porphyria cutanea tarda and disturbance of the liver function tests particularly the serum bilirubin. The association between rifampicin and porphyria cutanea tarda has not previously been described but might be expected because of the ability of rifampicin to induce various liver enzyme systems including delta aminolevulinic acid synthetase activity. This further illustration of rifampicin hepatotoxicity emphasizes the need for regular monitoring of liver function when rifampicin is prescribed. Rifampicin should be used with extreme caution in any patient with a previous history of porphyria cutanea tarda.

Case Report

A 55-year-old man presented with a short history of a left inguinal mass, weight loss of 7 kg and lumbar pain. Twenty-four years previously he had been treated for a tuberculous psoas abscess by bed rest, abscess aspiration and streptomycin for six months. Since then he had remained well with no history of liver disease and he admitted to an alcohol intake of only two or three pints of beer a week. He was taking no drugs and had no past history of skin rashes. Surgical exploration confirmed a recurrence of his tuberculous psoas abscess and a radiograph showed tuberculous disease of L4/5. Liver function tests were normal. Treatment was commenced with rifampicin 600 mg and isoniazid 300 mg in the form of Rimactazid-300 two tablets daily, taken on an empty stomach before breakfast, and he was discharged home.

Six weeks later he became jaundiced with pale loose stools and developed a generalized itchy bullous skin rash which was most prominent on his hands and face. Liver function tests showed a bilirubin of 59 mmol/litre (normal <17), alanine aminotransferase of 22 units/litre (normal <40) and alkaline phosphatase of 143 units/litre (normal <100). Rifampicin and isoniazid were discontinued. His skin rash settled within ten days but his liver function tests remained abnormal. Over the next few months the response to test doses of isoniazid and rifampicin was monitored (Fig. 1). There was little change in alkaline phosphatase and alanine aminotransferase levels in response to test doses, but worsening of his skin rash and elevation of serum bilirubin were clearly related to rifampicin ingestion. The skin reaction was characteristic of the cutaneous manifestation of porphyria cutanea tarda occurring in crops which appeared in large numbers following small doses of rifampicin and gradually receded when the drug was withdrawn. Biopsy of one of these lesions confirmed the presence of subepidermal blisters. Urinary porphyrins were measured later during a remission of the skin lesions and were normal. Further measurements of urinary and faecal porphyrins following repeated challenge by rifampicin were not felt to be justified.

Investigations of abnormal liver function included negative autoantibody tests with negative smooth muscle and antimitochondrial antibodies. Haemagglutination test for hepatitis B associated antigen was similarly negative. Haemoglobin, white blood count and differential, serum cholesterol, triglycerides and serum proteins were normal except for a diffuse rise in the gammaglobulin fraction. There was no evidence of inflammatory bowel disease. An oral cholecystogram performed when the serum bilirubin was only minimally elevated failed to opacify the gall-bladder. An intravenous cholangiogram showed numerous radiolucent stones within the gall-bladder and slight dilatation of the common bile duct.

Anti-tuberculosis chemotherapy was withdrawn and the skin rash receded while the liver function tests improved returning almost to normal. Five months after rifampicin had been discontinued an elective cholecystectomy was performed when the gall-bladder was found to be full of small gall-stones. The common bile duct was slightly dilated, compatible with previous obstruction, although no stones were found in the duct at operative cholangiography. Pathological examination confirmed the operative findings of mild chronic cholecystitis and multiple gall-stones. A liver biopsy was taken. Histological examination showed a diffuse spurring of connective tissue septa extending from the portal triads disrupting the lobular structure: in conjunction with the irregular regenerative nodules the picture constituted an early micronodular cirrhosis. The portal triads exhibited marked fibrosis with a moderately dense lymphocytic pericholangetic infiltrate. Bile retention was evident at a hepatocyte level and many hepatocytes were ballooned and degenerate in appearance. The inflammatory infiltrate eroded the limiting plate.

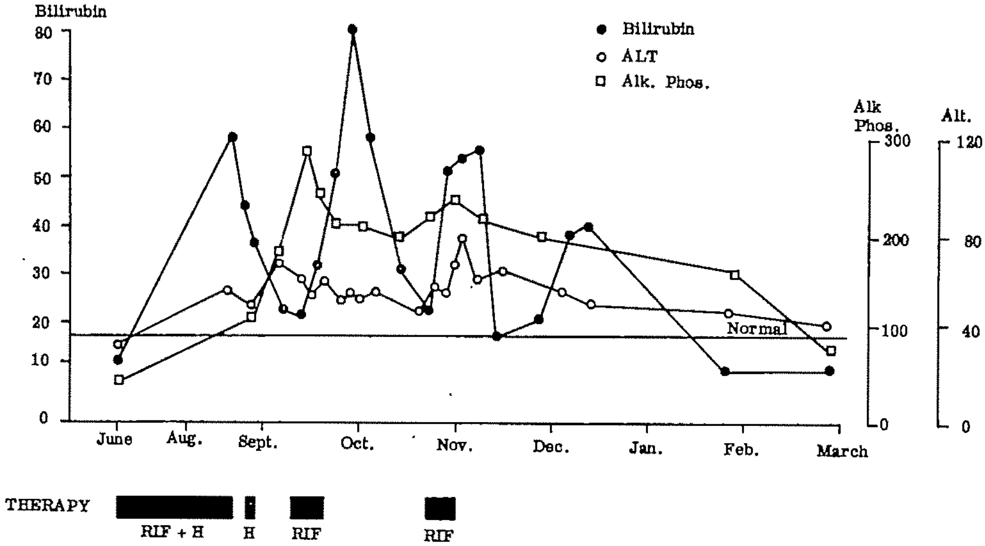

Fig. 1. Serial liver function tests over 10 months indicated the response to test doses of rifampicin. RIF = rifampicin; H = isoniazid; ALT = alanine aminotransferase.

The conclusion by several pathologists was that chronic cholangitis and pericholangitis could explain these findings, but that there was additional evidence of previous liver cell damage as evidenced by patchy areas of collapse of the reticulin with a mild inflammatory reaction and sparse collections of iron laden macrophages in the centrilobar zones. Although difficult to interpret, it was felt likely that these changes were secondary to a drug reaction, possibly in association with previous cholangitis.

The patient made a good recovery following cholecystectomy and one year later is well with only minor abnormalities of liver function on routine testing. He is not receiving any anti-tuberculosis chemotherapy and has had no recurrence of his skin lesions since discontinuing rifampicin.

DISCUSSION

The patient developed porphyria cutanea tarda and disturbed liver function tests following the administration of rifampicin and isoniazid. Subsequent test dosing on several occasions indicated that rifampicin precipitated the classical bullous subepidermal skin lesions of porphyria cutanea tarda and was also associated with acute increases in the serum bilirubin level with a more chronic disturbance of the serum alkaline phosphatase and alanine aminotransferase. Liver function tests prior to anti-tuberculosis chemotherapy were normal but the patient was subsequently shown to have cholelithiasis and may therefore have had a mild degree of preceding liver disease, although he gave no history suggestive of cholangitis. This pattern of hepatotoxicity and porphyria cutanea tarda has not been previously described in association with rifampicin therapy (Girling 1977).

Many drugs, including barbiturates, steroids, oestrogens and oral hypoglycaemics, may precipitate porphyria cutanea tarda (de Matteis 1967). The common underlying mechanism may be the induction of hepatic enzyme systems and in particular hepatic delta aminolevulinic acid synthetase (Davies 1977). Treece et al. (1976) reported a patient in whom pyrazinamide precipitated attacks of acute intermittent porphyria. Using rats as an animal model they demonstrated the ability of pyrazinamide to induce hepatic delta aminolevulinic acid synthetase activity. Other anti-tuberculosis drugs were studied and rifampicin also increased this enzyme activity, although to a lesser degree than pyrazinamide. The results suggested that rifampicin could precipitate porphyria in susceptible individuals.

Rifampicin must be incriminated in this patient because of the clear temporal relationship between the appearance of skin lesions and rifampicin ingestion but the presence of infection (Goldberg & Rimington 1962) and the possibility of preceding liver disease such as cholangitis secondary to cholelithiasis (Girling 1978) may have increased the risk of hepatotoxicity due to rifampicin. The appearance of the liver biopsy five months after rifampicin was discontinued was difficult to interpret but was compatible with a drug reaction superimposed on a background of changes secondary to cholangitis and biliary tract obstruction. The most striking abnormality in the liver function tests was a rise in bilirubin although the parallel rises in alanine aminotransferase and alkaline phosphatase did not suggest an obstructive aetiology. This disproportionate rise in bilirubin can be accounted for by the competition of rifampicin with bilirubin in the excretion of bile (Acocella et al. 1973).

Rifampicin must clearly be prescribed only with extreme caution to patients with known porphyria cutanea tarda or acute intermittent porphyria since induction of delta aminolevulinic acid synthetase enzyme systems can be expected to precipitate acute attacks of either condition. Rifampicin-based regimens are now the standard anti-tuberculosis chemotherapy in Great Britain so that the possibility of patients with previously unrecognized porphyria presenting with an acute attack precipitated by rifampicin should be considered.

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ACUTE GOUTY ARTHRITIS FOLLOWING ETHAMBUTOL THERAPY

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Summary

Two cases of ethambutol-induced hyperuricaemia associated with gouty arthralgia are reported. Withdrawal of ethambutol led to remission of symptoms in both cases.

INTRODUCTION

Hyperuricaemia following ethambutol administration has been documented (Postlethwaite et al. 1972, 1974; Postlethwaite & Kelley 1972), but, to the author's knowledge, there is only one report of three cases of acute gouty arthritis following ethambutol therapy (Self et al. 1977). I report two cases, who developed acute gouty arthritis following therapy with ethambutol along with other anti-tuberculosis drugs.

Case Report

Case 1

A 45-year-old woman was admitted to hospital on 6 February 1978 with a right-sided empyema. Before admission, she had been treated irregularly with streptomycin, INH, PAS and prednisolone with a provisional clinical diagnosis of pulmonary tuberculosis, but this had never been confirmed by sputum examination.

In the hospital, she was found to be very ill, with high temperature (39.4°C) and severe toxaemia. Chest radiography revealed massive (right-sided) pleural effusion. The left lung was normal. Diagnostic aspiration of the right chest revealed pus which was sterile on culture (after 48 hours of incubation), and culture for *M. tuberculosis* later, turned out to be negative. Repeated examination of sputum was negative for AFB.

A review of her chest radiographs taken before admission revealed a cavity in the right upper zone with infiltrates around it. A tentative clinical diagnosis of pulmonary tuberculosis (right-sided) leading to tuberculous empyema (right-sided) was made. Serum uric acid was 3.4 mg/dl. The patient was treated with intramuscular streptomycin (0.75 g) daily with isoniazid (300 mg) and ethambutol (800 mg; 20 mg/kg body weight per day) in a single dose after breakfast coupled with closed intercostal drainage and the right lung expanded in about a month. In the meantime, the patient started complaining of pains and aches all over her body, more so in her small joints. Serum uric acid was found to be 13.2 mg/dl. Blood urea remained normal. Ethambutol was withdrawn. The pain and aches quickly subsided. Serum uric acid, repeated after four weeks, was 3.2 mg/100 ml. Subsequently, she received streptomycin and isoniazid in the usual doses, and her recovery was uneventful.

Case 2

A 45-year-old woman came under the care of the author on 4 May 1978 with a history of alternating diarrhoea and constipation, pain in the abdomen, anorexia and low-grade pyrexia for six months. Examination of the abdomen revealed a vague lump in the right iliac fossa. Stools were repeatedly examined without success for worms, ova or cysts. She had received antiamoebic therapy irregularly for the last four months without obtaining much relief. Barium meal revealed a filling defect in the ileocaecal region and a tentative clinical diagnosis of ileocaecal tuberculosis was made.

The patient's serum uric acid was 4.2 mg/dl. She was given intramuscular streptomycin (0.75 g), isoniazid (300 mg) and ethambutol (900 mg = 20 mg/kg body weight) in a single daily dose. Within four weeks of initiation of therapy she started complaining of vague pains and aches all over her body, particularly in both knees. Both knee joints were slightly inflamed and tender. Serum uric acid was now found to be 11.5 mg/dl. Blood urea was normal. Ethambutol was withdrawn. The symptoms gradually subsided over the next four weeks. She was thereafter treated with streptomycin and isoniazid in usual doses without any adverse effect and the serum uric acid came down to 4.6 mg/dl.

DISCUSSION

Both cases developed a rise in serum uric acid, which appeared to be responsible for the gouty symptoms. Isoniazid could not be blamed for these symptoms because subsequent administration did not precipitate a rise in serum uric acid or joint symptoms, and the symptoms were not typical of those reported in isoniazid-induced arthritis (Periman & Venkatramani 1975).

A rise in serum uric acid during ethambutol therapy was reported by Postlethwaite et al. (1972), though this occurrence had earlier been denied by Place et al. (1966). Postlethwaite et al. (1972) conducted both prospective and retrospective studies on their cases and found a rise in serum uric acid ranging from 2.4 to 5.6 mg/dl in most of their cases. The rise was noted as early as 24 hours after the administration of a single dose of ethambutol or as late as 90 days after the initiation of therapy. However, most of the patients destined to show a significant increase in serum uric acid did so by the third week of therapy.

The rise in the serum uric acid in our cases was associated with the appearance of gouty symptoms at the end of four weeks of therapy, which, is in agreement with the observations of Postlethwaite et al. (1972).

The only other clinical case report of acute gouty arthritis associated with the use of ethambutol is by Self et al. (1977). Of three cases, one was also receiving pyrazinamide and the other hydrochlorothiazide. Though they attempted to exclude hydrochlorothiazide as being responsible for the elevated serum urate, they admitted that pyrazinamide was probably contributory.

Ethambutol therapy can not only lead to raised serum uric acid but also precipitate gouty arthritis.

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SPONTANEOUS PNEUMOTHORAX IN HODGKIN'S DISEASE

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Summary

Three cases of intrathoracic Hodgkin's disease are reported, in which spontaneous pneumothorax complicated the course of the disease. Factors related to this unusual complication are discussed.

Introduction

Lung involvement in Hodgkin's disease is well recognized and has been reported in 5 (MacDonald 1973) to 43% (MacDonald 1977) of cases, although origin in this site is rare (Kern et al. 1961). Pleural effusion is well documented (Peckham 1972) and pleural involvement was found by MacDonald (1977) in 38 (11%) of 284 patients. Although spontaneous pneumothorax has only rarely been reported in Hodgkin's disease (Kottler 1930; Croizat et al. 1959; Medrea et al. 1968), it occurred in three cases presenting at the Brompton Hospital over a 12-month period.

Case Reports

Case 1

A 20-year-old Jamaican woman presented with cervical lymphadenopathy and biopsy showed nodular sclerosing Hodgkin's disease. A lymphogram suggested abdominal lymph node involvement and the patient was staged IIIA. She received pulsed combination chemotherapy (mustine, vincristine, procarbazine, prednisone) for three months. Mediastinal and axillary lymph gland enlargement developed and treatment was changed to mantle irradiation (4000 r in four weeks), during which time the lungs received approximately 1200 r.

A laparotomy and splenectomy were performed and were normal. There was radiological evidence of shrinkage and some consolidation of the right upper lobe at this time. She was treated with amoxycillin with some symptomatic improvement and was discharged.

Four weeks later she was re-admitted with severe breathlessness. Radiologically there was extensive bilateral confluent mottling in all areas with further shrinkage of the right upper lobe. On the seventh day after admission, and three months after mantle irradiation, a small left spontaneous pneumothorax occurred. This resolved without intervention. Transbronchial lung biopsy from the right lower lobe showed many alveoli containing eosinophilic material resembling hyaline membrane, and there were traces of intra-alveolar fibrosis. Sputum and biopsy specimens were negative for organisms.

The patient was treated with high-dose corticosteroids, broad-spectrum antibiotics, antituberculous therapy and pentamidine with cotrimoxazole (to cover the possibility of *Pneumocystis* infection). Her condition deteriorated and she died of respiratory failure at eleven days.

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Post-mortem examination revealed extensive infiltration of both lungs and pleura by Hodgkin's disease.

Case 2

A 37-year-old Greek man presented to the Brompton Hospital with his third left spontaneous pneumothorax in two years and his second in recent months. There was a three-year history of cervical lymph gland enlargement and biopsy in Greece had shown a lymphoma; treatment had been commenced with unknown cytotoxic agents. Bilateral patchy shadowing had been present on their radiographs for at least five months. Left parietal pleurectomy, mediastinal lymph node biopsies and lung biopsy were performed. The lymph nodes showed lymphocyte depleted Hodgkin's disease and the lung biopsy showed a chronic inflammatory cell infiltrate only. No infective cause was found. The patient was re-started on chemotherapy and remains well.

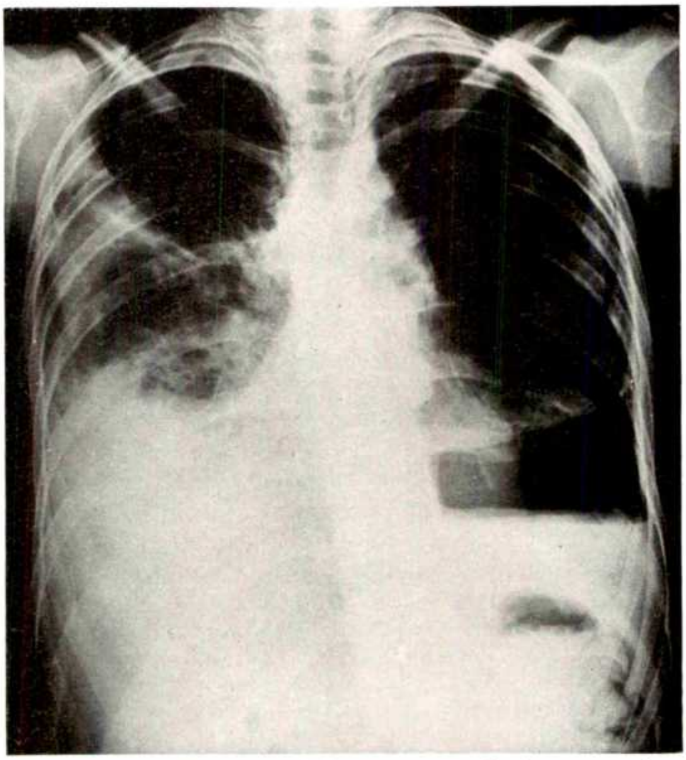

Fig. 1. Case 3: Chest radiograph showing left spontaneous hydropneumothorax and extensive right lung infiltration by Hodgkin's disease

Case 3

A 26-year-old English woman presented with axillary lymph node enlargement; biopsy showed nodular sclerosing Hodgkin's disease and she was subsequently staged IIA. She received mantle radiotherapy (3500 r in three and a half weeks). Subsequent laparotomy demonstrated abdominal lymph node involvement and combination chemotherapy was commenced. Owing to non-compliance with treatment, incomplete drug regimens were administered during the nine months prior to her presentation, including bleomycin up to a total of 100 mg.

In August 1975 bilateral pleural effusions and patchy consolidation in the left lower zone were noted on the radiograph. The pulmonary shadowing increased over the next year; she then developed a spontaneous left pneumothorax (Fig. 1) which was treated by tube drainage. The cause of the lung shadowing was not established by aspiration or by pleural or transbronchial biopsies but the shadowing paralleled the course of the Hodgkin's disease elsewhere.

The patient was treated for pulmonary Hodgkin's disease and opportunistic infections, but quickly died of respiratory failure. Permission for a necropsy was refused.

DISCUSSION

Pulmonary involvement in Hodgkin's disease is increasingly recognized (MacDonald 1977). One of the commonest radiological appearances is patchy consolidation associated with an infiltrative lesion, but single, multiple or exceptionally miliary nodules may occur, and cavitation within such nodules is documented (Lesobre et al. 1974). Recently, the importance of lung involvement adjacent to and radiating from enlarged hilar and mediastinal glands has been stressed (Peckham 1972).

Pleural involvement by Hodgkin's disease is often manifested by pleural effusions but spontaneous pneumothorax is a rare association (Medrea et al. 1969). No pneumothorax was described in two recent large reviews of intrathoracic involvement by Hodgkin's disease (Peckham 1972; MacDonald 1977). In our first patient there was necropsy evidence of extensive bilateral lung and pleural involvement by Hodgkin's disease. However, 12 weeks before the patient's terminal illness, she had received a modest dose of irradiation to the lungs and the shrinkage of the right upper lobe was consistent with radiation pneumonitis (Warren & Spencer 1949). Pneumothorax is a rare complication of thoracic radiation therapy for Hodgkin's disease (Libshitz & Banner 1974), although the interval between irradiation and pneumothorax was longer in their cases (eight and five months).

Our second patient, a man in whom Hodgkin's disease had been previously inadequately treated, developed three pneumothoraces on the same side within a two year period. The radiological appearances were consistent with pleural and/or lung involvement, although the specimen obtained at biopsy failed to confirm Hodgkin's disease in that part of the lung and pleura.

The pulmonary pathology of the third case also remains unproven. Her spontaneous pneumothorax occurred five and a half years after her mantle radiotherapy and after a year in which pleural effusions and pulmonary shadowing had progressed *pari passu* with her disseminated Hodgkin's disease.

There is good circumstantial evidence that pulmonary Hodgkin's disease caused the pneumothoraces in Cases 2 and 3. In two of our patients pneumothorax occurred after mantle radiotherapy (12 weeks and five and a half years) but in a third there was no irradiation treatment. All, however, had received chemotherapy, unlike the two cases reported by Libshitz and Banner (1974) who had had radiotherapy alone.

We conclude that spontaneous pneumothorax is a rare complication of Hodgkin's disease and that mediastinal radiotherapy may be a predisposing factor. The influence of chemotherapy is unknown.

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Br. J. Dis. Chest (1980) *74*, 415

THE BRITISH THORACIC ASSOCIATION

A meeting was held at Lillehammer, Norway, on 3–6 September, 1980, in conjunction with the Norwegian Thoracic Society. The following papers were presented:

Diagnosis and Management of Pulmonary Aspergillosis in Patients with Acute Leukaemia

G. K. Knowles, M. Slevin, M. J. Phillips, T. A. Lister and R. J. Davies

St Bartholomew's Hospital, London

Pulmonary aspergillosis is well recognized to occur in the immunologically compromised host but is uncommonly reported in the United Kingdom. Diagnosis is frequently delayed until post-mortem. Within a 12-month period three patients with acute leukaemia who had recently started chemotherapy developed pulmonary shadowing with rapid development of an air crescent picture typically associated with mycetoma formation. This sign was observed on tomograms in one patient who showed homogeneous shadowing on the routine chest radiograph. One or more *Aspergillus* species were cultured from sputum, transtracheal aspirates and/or specimens obtained at fibreoptic bronchoscopy in all cases. In one patient transbronchial lung biopsy confirmed invasive aspergillosis and in another appearances consistent with the wall of a fungal cavity were observed. The infection was confined to the lungs in each case.

All three patients responded to treatment of leukaemia with regression of lung shadowing and all are alive, in one case up to 16 months later. Two patients received the antifungal agent ketoconazole but the third recovered without specific antifungal therapy. Precipitins to *Aspergillus* species were negative in serial specimens of serum from each patient but in one in whom *Aspergillus fumigatus* was cultured, an enzyme-linked immunosorbent assay (ELISA) demonstrated a dramatic rise in serum IgG antibody to this species.

The value of tomography, fibreoptic bronchoscopy and the ELISA technique in the early diagnosis of *Aspergillus* infection in patients with leukaemia was discussed. The infection may be more common than hitherto suspected and its occurrence is compatible with prolonged survival.

Six Months Chemotherapy in Pulmonary Tuberculosis: A Controlled Trial by the British Thoracic Association

I. A. Campbell

Llandough Hospital, Cardiff

In this study of patients with culture-positive pulmonary tuberculosis isoniazid and rifampicin were given daily for six months, with an initial two-month intensive phase of streptomycin and pyrazinamide (SHRZ 6 regimen) or ethambutol and pyrazinamide (EHRZ 6 regimen). These were compared with a regimen of isoniazid and rifampicin for nine months supplemented by ethambutol for the first two months (EHR 9).

Of 511 patients starting chemotherapy 444 completed treatment according to the protocol. Significantly more patients receiving the pyrazinamide-containing regimens were culture-negative at two months (77%) than in the EHR 9 group (64%). A difference was still evident at three months (98% *vs* 88%). The conversion rates of the SHRZ and EHRZ groups were virtually identical. All patients in the three groups were culture negative by the end of the fifth month of treatment. Hepatitis occurred in 4% of the patients in each group. Other adverse reactions were commoner in the pyrazinamide-containing regimens. In the three groups between 0.6% and 2% of patients have relapsed after the end of treatment.

Isoniazid Plus Ethambutol in Continuation Antituberculous Treatment

A. W. Lees

Ruchill Hospital, Glasgow

A controlled trial carried out in Ruchill Hospital indicated that if pulmonary tuberculosis were treated initially with isoniazid, rifampicin and ethambutol, the continuation phase of treatment could be as effectively and more cheaply carried out with isoniazid plus ethambutol as with isoniazid plus rifampicin. The total duration of treatment was, however, one year and BTA trials have shown that, using isoniazid and rifampicin throughout, nine months are sufficient.

In the present trial patients admitted to hospital with bacteriologically positive pulmonary tuberculosis were routinely treated with isoniazid, rifampicin and ethambutol initially and nine months total treatment completed with isoniazid and ethambutol. Rifampicin was given initially for two, three or four months according to the estimated severity of the disease. So far patients have been followed up for at least one year after completion of treatment and there have been no relapses.

The Penetration of Cefuroxime into Pleural Fluid

A. D. Blainey, O. C. Finnegan and I. A. Campbell

Bristol Royal Infirmary and Llandough Hospital, Cardiff

Antibiotics, including cephalosporins, penetrate into pleural fluid to a variable extent. Cefuroxime, which is a broad-spectrum cephalosporin antibiotic with relative stability to β-lactamase, has not been fully investigated in this respect although it has been recommended for use in infections of the respiratory tract.

We have studied the intrapleural penetration of cefuroxime after the intravenous injection of 1500 mg in seven patients with pleural effusions of differing aetiologies. Serum, pleural fluid and urinary levels of cefuroxime were measured for seven hours after intravenous injection. We found that the rate of penetration of cefuroxime and the peak levels achieved were variable. The amount of antibiotic passing into the pleural cavity was dependent on the maximal serum levels achieved after intravenous injection, but was not related to pleural fluid protein concentration, the pathology underlying the pleural effusion or the differences in renal function. In all patients the peak antibiotic levels in the pleural fluid exceeded the minimum inhibitory concentration for common sensitive respiratory pathogens.

Please Listen to the Patient

Peter Stradling

A bronchoscopic colour picture show was presented, showing lesions that were missed because physicians did not listen to the patients' history or failed to examine them properly.

The Effects of Fenoterol, Ipratropium Bromide and Their Combination in Asthma and Chronic Bronchitis

G. Anderson, A. G. Jariwalla and P. Turnbull

St Woolos Hospital, Gwent

In a double-blind cross-over trial ten asthmatic and ten bronchitis patients each inhaled ipratropium bromide, fenoterol and both drugs together. In the asthmatic group the combined drugs produced an increase in peak expiratory flow rate approximating to that of the sum of each drug individually. In the bronchitis patients the increase in peak expiratory flow rate was less than the sum of that with the individual drugs, probably because of a more limited ability to respond to bronchodilators. The results suggest an anatomical overlap in the bronchial tree of vagal and adrenergic receptors.

A Comparison of Erythromycin, Co-trimoxazole and Amoxycillin in Patients Admitted to Hospital with Acute Exacerbations of Chronic Bronchitis

G. K. Knowles, A. F. Turner
I. W. Fawcett and R. J. Davies

St Bartholomew's Hospital, London

A comparative study of erythromycin stearate 500 mg three times daily, co-trimoxazole two tablets twice daily and amoxycillin 500 mg three times daily was performed in 70 patients with MRC chronic bronchitis admitted to hospital with an acute exacerbation of the disease. The latter was defined as an increase in cough, breathlessness and volume of sputum with alteration in sputum colour to yellow or green. Patients were selected to exclude those with a history of sensitivity to penicillin, amoxycillin, co-trimoxazole, sulphonamides or erythromycin, those with persistently purulent sputum, those with radiographic evidence of pneumonia and those with known malignancy.

The response to these regimen was monitored by daily clinical assessment including visual analogue scale recording of general state and respiratory symptoms by the patients themselves. Sputum volume and purulence, assessed macroscopically and microscopically, was noted each day. Changes in PEFR, FEV_1 and FVC and sputum bacteriology findings between admission and discharge were also recorded. Special attention was paid to side-effects of the three regimens.

The results of the study were presented.

Influence of High-Viscosity Sputum on Lung Function in Chronic Bronchitis

Arne O. Jenssen

Regionsykehuset, Trondheim

In ten patients with chronic obstructive bronchitis who were all kept on an unchanged maintenance medication and in a steady state of disease, sputum was collected from 8 a.m. until 12 noon The mean apparent viscosities of the collections were determined by a constant-flow tube system. PEFR was registered and spirometry was performed. Arterial blood gas analyses were accomplished immediately after the spirometry. All procedures were carried out within a week on three different days. The highest and the lowest readings of relative mean apparent viscosity in each patient together with the corresponding relative spirometric and blood gas data were chosen for statistical analysis. It was shown that a high mean apparent viscosity of sputum coincided significantly with deteriorated airway obstruction and also with significantly elevated $P\text{CO}_2$ and lowered $P\text{O}_2$.

Efficacy of Nifedipine in the Treatment of Angina Pectoris and Chronic Airways Obstruction

S. S. Jaiprakash, J. N. Sahay and S. S. Chatterjee

Wythenshawe Hospital, Manchester

Twenty patients suffering from angina pectoris with coexisting fixed or labile obstructive airways disease were given fortnightly treatments with nifedipine 10 mg three times a day or matching placebo over an eight-week period. Patients were allowed to continue their maintenance treatment for their obstructive airways disease throughout. All anti-anginal therapy except glyceryl trinitrate was withdrawn over 10–14 days before entry into the trial.

During the first placebo phase, patients were randomized to receive on separate visits a single dose of nifedipine or placebo before lung function tests (whole body plethysmograph) and blood pressure determination at 15-minute intervals for 90 minutes. FEV_1, FVC and AWR were unaffected by a single dose of nifedipine but PEFR was increased ($P<0.005$) compared with placebo at 90 minutes. Nifedipine reduced ($P<0.005$) systolic and diastolic blood pressure at 90 minutes compared with placebo.

In the 17 patients completing the protocol, after two weeks' treatments with nifedipine, FEV_1 increased ($P<0.05$), as did PEFR ($P<0.02$) in patients with labile obstructive airways disease, compared with placebo. Subjectively, angina pectoris was improved by nifedipine, which also increased ($P<0.01$) exercise tolerance during fortnightly treadmill exercise. Nifedipine appears to be an effective and safe anti-anginal in patients with coexisting obstructive airways disease.

Reversal of Inspiratory Airflow Obstruction after Nebulized Salbutamol: Its Importance in Patients with Irreversible Expiratory Airflow Obstruction

S. J. Connellan and S. E. Gough

Hammersmith Hospital, London

The acute effects of 10 mg of nebulized salbutamol on lung mechanics and exercise tolerance have been measured in 10 patients considered, by conventional assessment, to have severe irreversible airflow obstruction.

All had been heavy cigarette smokers and the mean FEV$_1$/VC% was 29%.

After nebulized salbutamol, VC improved much more than FEV$_1$ (21.6% and 5.1% respectively). The increase in maximum inspiratory flow at 50% of VC and peak inspiratory flow was much greater than that in maximum expiratory flow at 50% of VC and peak expiratory flow. Dynamic compliance and inspiratory and expiratory pulmonary resistance improved. Exercise tolerance using a modification of the 12-minute walk test showed an improvement on a pre-therapy walk of 56%.

It is suggested that improvements in inspiratory airflow obstruction and resistance with increase in VC and exercise tolerance may help further in deciding which patients will derive benefit from bronchodilator therapy.

Distribution of Flow Resistance in Patients with Airflow Limitation

B. Johansen

Rikshospitalet, Oslo

Gas-density dependence of forced expiratory flow was used to assess the distribution of airway resistance in patients with overt airflow limitation. Subjects with bronchial asthma increased their flow values more than 30% over most of the vital capacity range when helium–oxygen was breathed compared with air breathing, consistent with a predominantly central location of the airway resistance. In some of the subjects, density dependence decreased after inhalation of a beta-adrenergic aerosol, indicating preferential dilatation of large airways and persistence of obstruction in small ones. Subsequent systemic administration of the drug made density dependence reappear in some patients. Gas-density dependence tests, by partitioning resistance in central and peripheral component, may be useful in the assessment of the bronchodilating effect of various drugs.

Dyspnoea in 'Pink Puffers': The Place of Diazepam

P. Mitchell-Heggs and A. Guz

Epsom District Hospital, Surrey;
Charing Cross Hospital, London

Four patients with the 'pink puffer syndrome', usually associated with emphysema, who were not hypercapnic or severely hypoxic at rest, were treated with diazepam in moderate doses by a placebo-controlled, single-blind study, in an attempt to alleviate their breathlessness. On treatment, their effort tolerance improved and they experienced a striking reduction in dyspnoea; there was a reduction in the slope of the ventilation/CO$_2$ response curve in all subjects. The resting blood gases were unchanged. Psychiatric examination at the end of the study showed that, although these patients were depressed, prominent anxiety was a not a feature. It was concluded that diazepam may have a place in the management of dyspnoea in the 'pink puffer syndrome', but is only safe in the absence of any acute infection. The effect of diazepam on the ventilation/CO$_2$ response curve in normals was also discussed.

Non-malignant Pleural Disease and Asbestos

W. H. R. Smith and D. Davies

There is much confusion about the pleural disorders associated with asbestos exposure. The following classification was proposed: (1) visceral and parietal thickening associated with asbestosis; (2) parietal plaques; (3) pleural effusions; (4) constrictive or obliterative pleuritis; and (5) combined forms. The types were illustrated with particular attention to (4) which may develop after mild exposure and produce increasing disability.

Cardiac Dysrhythmias during Fibreoptic Bronchoscopy: Effects of Premedication with Oxprenolol

N. N. Stanley

Lister Hospital, Stevenage

Major complications during fibreoptic bronchoscopy are unusual, but deaths have been reported, several of which were cardiac in origin. In this study the electrocardiogram was recorded in 105 patients undergoing transnasal fibreoptic bronchoscopy. Premedication usually included atropine (0.6–1.2 mg), diamorphine (5–10 mg) and diazepam (5–10 mg) with the double-blind administration of oxprenolol (40 mg) to 51 cases and matching placebo to the 54 others: patients with a history of asthma were excluded from the study.

Mean heart rates before premedication,

after premedication but immediately before bronchoscopy and during bronchoscopy were 82, 101 and 116 beats/minute in those given placebo compared with 81, 86 and 94 beats/minute in those treated with oxprenolol. Heart rate during bronchoscopy exceeded 120 beats/minute in 22 cases given placebo and in only two cases after oxprenolol administration. Rise in blood pressure during bronchoscopy was minimized by oxprenolol. Ventricular ectopic beats were evident in 28% of cases before premedication; during bronchoscopy they occurred in only 21% of cases who received oxprenolol, but in 61% of those given placebo. Mean peak flow rate beforehand (324 litres/minute) was not altered by premedication with oxprenolol; a subsequent slight fall to 294 litres/minute after bronchoscopy was not significantly more than in cases who had not received oxprenolol.

The findings suggest that the electrocardiogram should be monitored in cases with heart disease undergoing fibreoptic bronchoscopy and that premedication with an antiarrhythmic agent such as oxprenolol may also be indicated in some of them.

Sweat Tests in the Diagnosis of Cystic Fibrosis in Adults

Margaret E. Hodson, Irene Beldon,
Ruth Towler, May Bamber and
J. C. Batten

Cardiothoracic Institute and Brompton
Hospital, London

The sweat test is accepted as a useful diagnostic test for cystic fibrosis in childhood. Normal adults have a higher sweat sodium concentration than normal children and the test may therefore be less reliable in adults. However, some authors take the upper limit of normal sweat sodium in adults of 60 mmol/litre and others even say that one can 'interpret the sweat test results in adults with the same degree of reliability as in children'. Modifications of the sweat test for adults giving the patient aldosterone or fluorohydrocortisone have been advocated. However, most of the reports concern children rather than adults.

Sweat tests have therefore been performed in 18 adolescents and adults (age range 15–36 years) and 23 normal controls (age range 19–40 years) and the response to the sweat sodium to two days of treatment with fluorohydrocortisone has been recorded. Sweat tests were performed using pilocarpine iontophoresis and the sodium measured by flame photometry.

The results obtained (mean ±2 SD) were as follows: Sweat sodium (mmol/litre): controls 44.9 (±35.0), CF patients 106.1 (±32.6) ($P<0.001$). Suppression following fluorohydrocortisone (%): controls 24.2 (±30.1), CF patients 9.3 (±18.6) ($P<0.001$). Level of sweat sodium (mmol/litre) after suppression: controls 33.7 (±27.1), CF patients 98.7 (±31.4) ($P<0.001$).

Three of the 23 normal adults had sweat sodium concentrations of over 60 mmol/litre so the sweat sodium concentrations in adults are a less reliable diagnostic test than in children. Using the suppression test not one of the adult CF patients sweat sodium suppressed below 70 mmol/litre but all the normal controls suppressed below this value. Using statistical methods to investigate the overlap between the distributions it can be shown that if the level of the sweat sodium alone is used to diagnose CF in adults 3.6% of patients will be misdiagnosed but using the level to which the sweat sodium can be suppressed only 1.3% will be misdiagnosed. The fluorohydrocortisone suppression test therefore appears to be a useful test in adults suspected of having cystic fibrosis.

A Comparison of Aerosol and Powder Inhalation of Beclomethasone

I. A. Campbell, O. C. Finnegan,
Jeanette Todd and Denise Smith

Bristol Royal Infirmary and Frenchay
Hospital, Bristol

Twenty-six patients with chronic steroid-dependent asthma were studied comparing the effect of 400 μg daily of beclomethasone dipropionate delivered by conventional pressurized aerosol with the effect of the same dose as dry powder delivered by a rotahaler. Airflow obstruction was assessed by serial peak expiratory flow rate measurements and daily diary cards. Overall the two preparations were equally effective. This was also true in the 13 patients whose technique with the conventional pressurized aerosol was mediocre or poor. Six of the 26 patients preferred the rotahaler.

It is concluded that beclomethasone dipropionate powder via a rotahaler is equally effective weight for weight as via the pressurized aerosol. The rotahaler did not improve control of asthma in those of our patients whose technique with the pressurized inhaler was inadequate.

An Evaluation of Sustained-Release Aminophylline in Exercise-induced Asthma

M. J. Phillips, S. Ollier,
P. W. Trembath, S. W. Boobis and
R. J. Davies

St Bartholomew's Hospital, London

A group of nine young adult asthmatic patients were given placebo and sustained-release aminophyllin tablets for one-week periods in a double-blind random order cross-over study. Morning and afternoon exercise tests were performed at the end of each week period and the maximum falls in PEFR following exercise were compared.

Sustained-release aminophylline was significantly better than placebo at inhibiting exercise-induced asthma, with a maximum fall in PEFR for the group of $13.3 \pm 3.6\%$ (mean ± SE) in the morning compared with $29.6 \pm 5.6\%$ when on placebo ($P<0.01$) and $18.6 \pm 2.5\%$ in the afternoon compared with $28.5 \pm 5.6\%$ when on placebo ($P<0.05$) and resulted in mean plasma theophylline levels of 10.8 μg/ml and 11.2 μg/ml respectively.

Gastro-Oesophageal Reflux and Bronchial Asthma

A. Bernstein

Hope Hospital, Salford

Evidence has been accumulated to suggest that gastro-oesophageal reflux may act as a trigger in patients with bronchial asthma leading to a worsening of respiratory symptoms and conversely that surgical or medical relief of gastro-oesophageal reflux may produce a considerable improvement in respiratory symptoms in some of these patients.

Twenty patients with bronchial asthma who also had symptomatic gastro-oesophageal reflux were investigated: 17 were considered to have late-onset asthma. The severity of their reflux was graded on symptom score of heartburn, regurgitation or both and by barium swallow and meal, fibreoptic endoscopy and biopsy, manometry and pH monitoring of the distal oesophagus and an acid infusion test. Full lung function studies were performed and patients were entered into a double-blind cross-over study using cimetidine as the antireflux agent.

Eighteen patients completed the study. Significant improvements were seen in reflux symptoms and night time asthmatic symptoms, both these indices being measured on a scoring system. Home monitoring of peak flow values showed a statistical improvement for the last peak flow reading of the day. Fourteen patients felt that their chest symptoms had significantly improved during the cimetidine period. Computer analysis of the data revealed that during the period on placebo tablets there was a correlation between the severity of both reflux and asthmatic symptoms during the day and the night. There was no such correlation during cimetidine therapy.

Bronchodilator Properties of Inhaled Clemastine

R. D. H. Monie, J. P. White,
P. D. J. Handslip, J. P. R. Hartley
and S. G. Nogrady

Llandough Hospital, South Glamorgan

The bronchodilator properties of the H_1 receptor antagonist, clemastine, when delivered by a standard metered aerosol were investigated in this study. The side effects of oral and inhaled antihistamines have previously limited their use in the management of asthma.

Eleven asthmatic patients, convalescing from an exacerbation of bronchial asthma, participated. On three consecutive mornings base-line measurements of FEV_1 were recorded (the base-line measurements each morning were within 15% of each other). Each patient inhaled 20 or 200 μg of clemastine or placebo in a random double-blind fashion and FEV_1 was then monitored for six hours after each inhalation.

There was a gradual rise in FEV_1 following inhalation of 200 μg of clemastine to reach a maximum increase of 23.7% (mean of individual peak values). The maximum increase following 20 μg of clemastine was 15.4% while that following placebo was 6.8%. These peak values in FEV_1 were significantly different ($P<0.05$, paired t-test).

The rise in FEV_1 reached statistical significance after 90 and 120 minutes following inhalation of 200 and 20 μg respectively of clemastine, whilst the peak values occurred between three and four hours.

The only comment from patients was the unpleasant taste of the inhaled clemastine. No other side effects were noted.

Cardiorespiratory Adjustments during Near-maximal Exercise in Patients with Chronic Obstructive Lung Disease

J. SCHAANNING

Regionskehuset, Trondheim

The mechanism of reduction of the exercise capacity in patients with chronic obstructive lung disease was studied. The bellow function had strong influence on the exercise capacity.

The respiratory dead space/tidal volume ratio was negatively correlated with the exercise capacity, otherwise no limitation was found in parameters of gas exchange. A low stroke index with normal cardiac index, when related to oxygen consumption, was present in the patients with low exercise capacity. Stroke index was associated with the degree of airway obstruction, not with gas exchange parameters.

Hyperinflation with short inspiratory time and high air flow rates characterizes patients with low exercise capacity. Volume/inspiratory time diagrams were similar for patients and normal subjects.

The effects of cardioselective beta-blocking agents on some of the parameters were discussed.

Is the Inspiratory Limb of the Flow-Volume Loop Worth Recording?

D. M. DENISON, J. F. WALLER,
C. W. G. TURTON, T. SOPWITH
AND D. J. BROWN

Brompton Hospital, London

The major part of the expiratory limb of the maximal flow–volume loop is independent of effort, highly reproducible and determined by the mechanical characteristics of the alveoli and airways alone. Thus this limb has a high information content and is valuable clinically. It is often argued that the inspiratory limb, which is effort-dependent, is less reproducible and contains little information of clinical value. We have examined a total of more than 10 000 complete flow–volume loops, obtained from a wide variety of patients in this laboratory, and wish to challenge that view. All loops conforming to any of three shape criteria were selected and the functional and clinical features of the patient at that time were noted. The criteria were: (1) mid-expiratory flow greater than mid-inspiratory flow, (2) mid-inspiratory flow greater than 10 times the mid-expiratory flow and (3) late-inspiratory flow less than 0.67 times the early-inspiratory flow. Information on the predictive value of these shapes was presented. In principle, shape (1) indicates a restrictive process, upper airways obstruction or inspiratory neuro-muscular weakness, shape (2) suggests emphysema and shape (3) implies a particular form of uneven ventilation.

Flow–Volume Indices Obtained with a Vitalograph Spirometer

W. H. PERKS, R. B. COLE, K. PROWSE,
A. EVANS, M. MACKINTOSH, N. C. NEVEN,
P. JONES AND M. GREEN

North Staffs Hospital Medical Centre,
Stoke-on-Trent; Keele University; and
Brompton Hospital, London

Flow at 75%, 50% and 25% of the vital capacity was measured by drawing tangents on simple spirometric curves obtained during forced vital capacity manoeuvres on a Vitalograph spirometer. In 19 trained normal subjects and 33 patients, values obtained by this technique were read blind and compared to flow rates obtained from an Ohio 840 spirometer. There were minimal differences between values obtained by the two techniques and the correlations were good (V_{max75}, V_{max50} and V_{max25}: in normals $r=0.88$, 0.96 and 0.95; and in patients $r=0.89$, 0.91 and 0.93 respectively). There was no significant between-observer or within-observer variation. In six normal subjects the mean within-subject coefficients of variation over six days was similar to other techniques of obtaining flow–volume data (V_{max75} 8.3, V_{max50} 8.1 and V_{max25} 10.6).

Normal values were obtained in 553 and 488 asymptomatic working males and females respectively. The shape of the maximum expiratory flow–volume curve constructed from the mean values became more convex with age with both smokers and non-smokers. The regression of variables against age showed a significant fall in forced vital capacity and $V_{max\,50}$ in asymptomatic male smokers and $V_{max\,75}$ in asymptomatic female smokers.

We have found this technique of obtaining flow–volume data and the normal regression equations valuable in epidemiological surveys of occupational lung disease. It is simple, cheap and reproducible and the values obtained discriminate better between affected and unaffected workers than the standard spirometric measurements.

Sleep Apnoea in Diabetic Patients with Autonomic Neuropathy

P. J. Rees, J. G. Prior, G. M. Cochrane and T. J. H. Clark

Guy's Hospital, London

Diabetic patients with autonomic neuropathy have a poor prognosis and unexpected cardiorespiratory arrests have been reported in such patients in association with anaesthesia and pneumonia. This suggests that these patients may have abnormal ventilatory control. We have studied the pattern of breathing during sleep in eight diabetic patients with autonomic neuropathy and in eight without neuropathy, matched for age and sex.

Autonomic neuropathy was assessed by the effect of posture and respiration on pulse and blood pressure. All patients were on subcutaneous insulin and their diabetes was well controlled at the time of the study. Patients were studied through one night's sleep in a quiet room while airflow at nose and mouth was monitored with thermistors, ribcage and abdominal movement with magnetometers and an electrocardiogram was performed.

Three diabetic patients with neuropathy had more than 30 periods of apnoea lasting more than ten seconds during one night's sleep (range 32–73). Two of these had predominantly central and one predominantly obstructive apnoeas. Blood glucose measurements during the night in one patient with apnoea showed no evidence of nocturnal hypoglycaemia. The maximum number of apnoeas in a diabetic without neuropathy was eight in one night.

The apnoeas may predispose these patients to unexpected cardiorespiratory arrests when there are additional factors such as respiratory depressant drugs during anaesthesia or hypoxia during respiratory illnesses. They might also contribute to the microvascular complications which were more common in our patients with autonomic neuropathy.

Prednisolone Metabolism and Chronic Blood Gas Disturbance

W. A. C. McAllister, J. V. Collins and J. Efthimiou

Brompton Hospital, London

Many respiratory patients treated with prednisolone have chronic arterial blood gas disturbances. Enzymatic oxidation of prednisolone and other drugs occurs in the liver. Blood gas changes are known to affect significantly the rate of biotransformation of drugs such as antipyrine and theophylline which undergo similar hepatic oxidative metabolism to prednisolone. This study investigated the effect of chronic arterial blood gas changes on the metabolism of prednisolone in respiratory patients. 12 chronically hypoxic patients with a variety of respiratory conditions were compared with normal subjects and non-hypoxic respiratory patients. All those studied were given 20 mg of oral prednisolone at 0800 after an over-night fast. No food was taken for two hours after the commencement of the study. For nine hours following ingestion of the drug, blood samples were taken for estimation of plasma prednisolone levels using a radio-immunoassay. Pharmacokinetic data, including area under the plasma concentration time curve, maximum plasma concentration, peak concentration time, volume of distribution, clearance and half-life, were all calculated. There was no difference in any of the parameters between hypoxic and non-hypoxic patients as a whole. However those hypoxic patients with CO_2 retention showed a significant increase ($P < 0.01$) in half-life of prednisolone as compared with the rest of the group. The average increase was 27%. The findings indicate that in the presence of chronic CO_2 retention dosage regimens of prednisolone should be altered accordingly.

Lung Function in Healthy Adults in the City of Oslo

A. GULSVIK

Rikshospitalet, Oslo

In a two-phase cross-sectional survey in Oslo 699 women and 556 men were examined with a Vitalograph dry spirometer. Of these, an asymptomatic group of healthy subjects aged 20–70 years comprised 140 women and 124 men.

In the asymptomatic group intra- and inter-subject variability of forced mid-expiratory flow ($FEF_{25-75\%}$) were three and two times higher, respectively, than those of vital capacity VC and FEV_1.

The frequency distribution of the spirometric variables did not differ significantly from a normal (Gaussian) distribution. VC, FEV_1 and $FEF_{25-75\%}$ decreased with age and increased with body height. At all ages men had higher values than women also after correcting for differences in body height.

The estimates of FEV_1 and $FEF_{25-75\%}$ in each decade of the target population were smaller than those of the asymptomatic group.. This difference was less marked in women, suggesting a more frequent occurrence of airflow limitation in men. Smokers in the asymptomatic group have impaired lung function compared with non-smokers.

Effect of Radiotherapy on Survival in Patients with Resected Lung Cancer with Stump or Mediastinal Node Involvement

M. R. LAW AND MARGARET E. HODSON

Brompton Hospital, London

Case notes of patients having had lobectomy or pneumonectomy as an attempted curative procedure for lung cancer were examined and cases of squamous or adenocarcinoma with malignant involvement of the bronchial stump or mediastinal lymph nodes selected. Excluded were perioperative deaths and cases with evidence of spread beyond that described above at surgery.

A proportion of patients with stump involvement or metastases to mediastinal lymph nodes had been given radiotherapy in the hope of prolonging survival. The effect of this was studied by comparing survival in this group with that of the remainder.

39 patients had mediastinal lymph node involvement. Seven of 25 patients with squamous cell histology had been given radiotherapy, as had seven of 14 patients with adenocarcinoma. Survival in the groups with and without radiotherapy (at one, two and three years) were similar, suggesting that radiotherapy does not prolong survival.

No patient with adenocarcinoma received radiotherapy for stump involvement. There were 18 cases of squamous cell carcinoma with stump involvement; 11 were given radiotherapy. Survival figures up to three years are similar. However four patients survived over four years, three of these for six years, and all of these had received radiotherapy. No patient with stump involvement who did not receive radiotherapy survived more than three years.

Carcinoembryonic Antigen/Complement and Lung Cancer

P. M. JOHANNESSEN AND H. HAUGLAND

Haukeland Sykehus, Bergen

Serum levels of carcinoembryonic antigen (CEA) were studied in a series of 85 patients with bronchogenic carcinoma. The group was subdivided according to histology and whether local or distant metastasis had occurred. In 30 patients serial CEA levels were measured and related to clinical development.

The results were compared with CEA levels in a control group comprising patients with different forms of non-malignant lung disease. A similar study was performed, measuring complement factors and immunoglobulins.

The Five-Year Results of a Controlled Study of BCG Immunotherapy after Surgical Resection in Bronchogenic Carcinoma

J. W. MILLAR, P. ROSCOE, S. PEARCE, S. LUDGATE AND N. W. HORNE

City Hospital, Edinburgh; and University of Edinburgh

Surgery remains the treatment of choice in patients with bronchogenic carcinoma with five-year survival rates of 20–40% in the minority suitable for operation. Almost all this mortality is due to metastases or recurrence of the primary tumour. Attempts to improve these figures have included post-operative non-specific immunotherapy to stimulate the patient's own immune system to prevent tumour recurrence but the results have been inconclusive.

We report the five-year results of a controlled study of BCG immunotherapy given postoperatively to a consecutive group of 90 patients with bronchogenic carcinoma treated by surgical resection. Patients were assigned to three treatment regimens: (1) control group (35 patients); (2) BCG via intradermal route (26 patients); and (3) BCG via multipuncture route (29 patients). Immunotherapy was repeated on seven occasions in the first postoperative year.

The overall five-year survival in all groups was 37%, with favourable prognostic features being squamous carcinoma (46% survival), the absence of involved mediastinal nodes at operation (46%) and lobectomy (40%) but even the presence of mediastinal nodes was associated with a 19% five-year survival. There were no significant differences between the groups treated by immunotherapy and the control group although there was a trend towards improved survival in patients with 'undifferentiated carcinoma' (30%) compared with control (18%) in keeping with the early results of a larger series treated with a single subdermal BCG injection. No serious side-effects of immunotherapy were encountered.

The role of BCG immunotherapy remains uncertain but it may have a place when given postoperatively to patients with undifferentiated large and small cell carcinoma.

BCG Plus Levamisole following Irradiation of Advanced Squamous Bronchial Carcinoma

A. Pines

East Herts Hospital, Hertford

Patients with squamous carcinoma of the bronchus with locally advanced and inoperable lesions, but without obvious metastases, were irradiated with a dose of at least 4000 rads in an attempt to bring about a cure.

An original series was randomized between controls and patients given BCG at two-weekly intervals. Survival was significantly better for the BCG-treated patients during the first year only. Three are still alive and well seven to nine years later. All control patients had died by the end of the third year. Metastases were common among control patients but not among the BCG-treated group.

To improve these results levamisole was given in addition in a dose of 2.5 mg/kg body weight on two days of the week. Treatment was allocated at random to three groups: control, BCG two-weekly and BCG four-weekly. At the end of the first year 44% of 27 controls, 50% of 16 patients given levamisole and BCG four-weekly and only 4% of 23 patients given levamisole and BCG two-weekly had died. At the end of the second year deaths were 66% among the control group and 22% in the levamisole and two-weekly BCG group. In the third year deaths were 85% and 74% respectively. The four-weekly BCG regimen had been discontinued. Skin testing with tuberculin and *Candida* showed some correlation with these results. There were many fewer metastases in the group given BCG two-weekly. BCG two-weekly thus appears to give some prolongation of life, though after two years there is no further benefit.

Tuberculosis in North Lincolnshire (South Humberside)

G. A. Batson

Scunthorpe General Hospital

This being the Viking Year in the United Kingdom, I thought it would be interesting to show very briefly the quite considerable influence the Vikings have had on the geographical distribution of villages of North Lincolnshire. The Scunthorpe district is geographically large but with a population of only around 200 000. Although there are now a reasonably significant number of newer immigrants from the Indian Subcontinent, by and large they have made no contribution whatever to the problem of tuberculosis. The actual figures are as follows:

Year	*Pulmonary*	*Non-pulmonary*	*Total*
1975	20	1	21
1976	13	1	14
1977	22	3	25
1978	20	3	23
1979	17	7	24

This basically means one new patient per fortnight over the past three years. For socio-economic reasons, as a result of the geography, we have re-instituted the Mass X-Ray Unit.

Prognosis of Lung Cancer Treated by Surgery

J. R. VALE AND H. ROSTAD

Rikshospitalet, Oslo

Of 1053 patients with primary lung cancer treated in Rikshospitalet, Oslo, 48% were primarily considered inoperable while a further 12% proved unresectable at thoracotomy. Survival rates (five years) were 36% and 2% in the resected and the non-resectable group respectively.

Prognostically favourable indices were a low age at the operation, the absence of symptoms, a peripheral localization of the tumour, lobectomy rather than pnemonectomy and the surgeon's stated assumption of a completely excised tumour. Thus a lobectomy considered complete gave 52% survival versus 9% in case of a pneumonectomy of doubtful radicalness.

The resected series included 27 patients with small cell anaplastic cancer of whom nine survived for five years without additional therapy.

Legionnaires' Disease—A Review

D. DAVIES

City Hospital, Nottingham

Since the dramatic epidemic in Philadelphia in 1976 many more outbreaks of Legionnaires' disease have been recognized. Earlier episodes of respiratory disease, going back as far as 1965, have also been attributed to *Legionella pneumophila*, retrospective diagnosis being made using stored sera. It now appears that the organism was first isolated in 1947 but it was not then recognized as a human pathogen. The epidemiology was reviewed.

Sporadic cases are occurring in many parts of the world. The distribution is patchy and there is an unexplained preponderance in Nottingham. The pointers to the diagnosis were outlined and suggestions made for early management of severe pneumonia.

FUTURE MEETINGS OF THE BTA

The list below gives details of future meetings, both arranged and provisionally planned, and we hope this will prevent the clashing of dates with meetings arranged by other societies.

29/30 January 1981	Jointly with the Thoracic Society at the Royal Free Hospital, London.
6/9 May 1981	Jointly with the Europe Region International Union Against Tuberculosis and the Chest, Heart and Stroke Association, Bournemouth.
January/February 1982	Jointly with the Thoracic Society. A two-day meeting at the Royal Free Hospital, London.
30 June/3 July 1982	Jointly with the Thoracic Society, University of York.
27/30 June 1983	Churchill College, University of Cambridge.
24/27 June 1985	Churchill College, University of Cambridge.

Further details of these meetings can be obtained from Dr G. Anderson, Newport Chest Clinic, 129 Stow Hill, Newport, Gwent NPT 4GA.

FUTURE MEETINGS OF THORACIC SOCIETY

29/30 January 1981	Jointly with the BTA at the Royal Free Hospital, London.
4/5 July 1981	Jointly with the Scottish Thoracic Society, St Andrews University.
January/February 1982	Jointly with the BTA. A two-day meeting at the Royal Free Hospital, London.
30 June/3 July 1982	Jointly with the BTA, University of York.

PAPERS INVITED

The British Thoracic Association and the Thoracic Society invites papers for presentation at the Joint Meeting on 29/30 January 1981 at the Royal Free Hospital, London. Summaries of 200–300 words should be submitted to the Honorary Secretary, Dr G. Anderson, Newport Chest Clinic, 129 Stow Hill, Newport, Gwent NPT 4GA by 24 October 1980.

The British Thoracic Association also invites papers for Joint Meeting with the IUAT and CHSA on 6/9 May 1981 at Bournemouth. Summaries of 100 words should be submitted to the Honorary Secretary, Dr G. Anderson, Newport Chest Clinic, 129 Stow Hill, Newport, Gwent NPT 4GA by 1 December 1980.

BOOK REVIEWS

Pediatric Bronchology

Edgár Székely and Edit Farkas

Baltimore: University Park Press (Lancaster: MTP Press). 1979. Pp. 628. Price £39.50

This book is a translation from the Hungarian of the authors' experience of bronchoscopy, bronchography and bronchial catheterization. There are 70 chapters devoted to the findings, primarily on bronchoscopy and bronchography, in all the conditions affecting the upper and lower airway which a paediatrician, bronchoscopically orientated or not, is likely to see in his professional lifetime. The chapters include 149 illustrative case histories and in addition there are chapters on the type of instruments available, the techniques of bronchoscopy and the anaesthetics used, and the bacteriology of bronchial aspirates.

The authors have carried out over 30 000 procedures during a 15-year period, which works out at about six to seven bronchoscopies per working day! Clearly one needs to know the indications for this enthusiastic use of endoscopy, but sadly this information is totally lacking.

The chapter on indications is merely a list of all the conditions affecting the respiratory tract! Even in the individual chapters, or case histories, it is far from clear to the British reader why a bronchoscopy or bronchography was performed. Why should one want to follow bronchoscopy with bronchography in diaphramatic eventration? —or indeed ever need to bronchoscope an asymptomatic asthmatic—yet over 1000 such patients were submitted to bronchoscopy. Where indications are given, e.g. aspirating tuberculous granulation tissue, or bronchoscopic instillation of mucolytics into the bronchial tree followed by aspiration of the dissolved material as the initial therapy for cystic fibrosis, they are totally at variance with practice in Britain. For this reason the book is of little value in assessing the place of these procedures and the diagnosis and therapy of paediatric respiratory disease.

It is, however, of some value as an atlas of the bronchoscopic and bronchographic findings in both common and uncommon respiratory disease. The section on malformations of the respiratory tract contains much that is of value, especially the catalogue of the normal variation in the branching of the bronchial trees. The value of the many radiographs and bronchograms is, however, seriously restricted by the fact that the specific lesion in the illustration is not indicated by an arrow or similar device, and to the non-radiologist no abnormality is apparent among the white efflorescence coming off the main bronchus. The legends to the diagrams and tables are particularly bad. For example Table 16 is unlabelled and indecipherable.

There are the usual problems with translation. I think I know what 'spastic bronchitis' and infantile 'hypotrophy' are, but what is 'colliquated'. what is the significance of a 'verminous' shadow, and when should a 'conicotomy' be carried out?

Libraries in hospitals with a big paediatric respiratory disease service might consider the book to be a worth while purchase, but with all the problems listed above, at £39.50, this publication cannot be recommended for the individual paediatrician or pulmonologist.

N. R. C. Roberton

Lung Biology in Health and Disease, 13. Evolution of the Respiratory Processes: A Comparative Approach

Stephen C. Wood and Claude Lenfant

New York: Marcel Dekker. 1979. Pp. xviii +370. Price SFr 90.00

The series of books published under the general heading of *Lung Biology in Health and Disease* has achieved a high reputation as providing a scientic background for the study of respiratory disorders and this volume maintains this established tradition.

This book is concerned mainly with the adaptations of the respiratory mechanisms to the change from an aquatic to an air breathing environment. But examples are considered from unicellular surface respiring organisms at one end of the scale to man and cattle at the other end. This work will be of interest primarily to biologists at undergraduate or early postgraduate level as it gives a stimulating introduction to further work that needs doing in the study of respiratory processes in animals in differing ecological situations and at different stages of evolution. This book is unlikely to appeal to the busy physician unless he has an interest in biology and evolution.

The seven chapters are each by different authors and cover different aspects. The first two cover breathing mechanisms and gas exchange, while the others deal with cardiovascular support of metabolic functions in vertebrates, oxygen transport, vertebrate acid–base regulation, cell metabolism and the origins of endothermy and the size of respiratory structures in mammals. All the authors have a wide experience in the field on which they have written. I suspect that only two of the authors met the editors' initial dead-line as their references do not go beyond 1976, while all the other authors include references up to 1978. There is also a further suggestion of haste in finalizing the book in that the indexing is somewhat erratic and a number of errors have escaped the proof reader.

P. G. I. Stovin

Manual of Pulmonary Function Testing

Gregg Ruppel

St Louis: C. V. Mosby (London: YB Medical Publishers). 2nd edition. 1979. Pp. x+162. Price £6.00

A good book of this size about pulmonary function tests would fill an important gap. These tests are not as widely used as they should be in general practice, in district general hospitals or even in many teaching hospitals outside the specialized chest departments. Increased use would follow greater understanding of the individual tests and wider appreciation of which tests are helpful in aiding the diagnosis and management of which particular diseases.

Books on this subject generally fall into one of two traps. Either they are written using specialist terminology (jargon?) or their authors fail to distinguish between tests which are clinically useful in the majority of respiratory diseases and those which provide interesting insights into the pathophysiology of the disease, but which rarely affect clinical decisions.

Dr Ruppel describes the techniques of a comprehensive list of tests clearly. I found the short sentences and short chapters easy to read. He assumes a 'rudimentary knowledge of physiology' which is a pity and a mistake. Many physicians have forgotten their rudimentary physiology and short sections explaining the processes whereby diseases produce abnormal results would be helpful.

My major adverse criticism of this book is the total lack of any discussion on the place of each test in clinical respiratory medicine. There are no clinical examples. In Chapter 7 he suggests that patients referred for tests in an (American) general hospital will have measurements made of the following: vital capacity, inspiratory capacity, expiratory reserve volume, functional residual capacity, residual volume, total lung capacity, RV/TLC ratio, tidal volume, respiratory rate, minute volume, respiratory dead space, alveolar ventilation, FVC, FEV, FEV_T, $FEV_{T\%}$, $FEF_{25\%-75\%}$, peak flow, MVV, flow volume curves, single breath N_2, 7-minute N_2 washout, transfer factor, blood gases, percentage shunt and V_D/V_T ratio. He gives no consideration as to which of these tests are useful and in which diseases. This reflects intellectual laziness and wastes a lot of money. You may imagine the battery to tests undergone by patients referred to the 'cardiopulmonary' laboratory.

I have some further particular criticisms. He almost ignores the peak flow meter (a cheap, useful British machine) until the section on testing children; he muddles flow-volume loops and curves and his illustration of a typical loop in intrathoracic tracheal obstruction is highly atypical; he states that 'the main limiting factor to diffusion is the status of the alveolar capillary membrane', almost ignoring the far more relevant factor of ventilation–perfusion relationships in the lungs; he mentions ventilation–perfusion imbalance as the *third* cause of hypoxia and fails to state that it is not imbalance but low ratios that are important.

I cannot recommend this book to students because there is too little physiology and almost total neglect of the real value of the tests described. It is clearly not a book that specialists in the field would wish to buy. For the reasons given this book is also of no value to general physicians who see patients with chest diseases.

B. D. W. Harrison

Principles and Practice of Blood Gas Analysis

A. P. Adams and C. E. W. Hahn

Morris Plains, NJ: General Diagnostics. 1979. Pp. 95. Price £8.00

A recent paper in the Journal, from McMaster University, reported widespread ignorance of the mechanisms leading to abnormalities of blood gases in clinical practice. Many physicians and anaesthetists will have come to the same conclusion in this country. This excellent book should go a long way toward correcting areas of uncertainty and ignorance in the clinical field of blood gases.

The first five chapters describe the physiology of normal and abnormal blood gases and pH. The text is generally very clear and the diagrams are excellent. In the chapter on oxygen transport there is an excellent section on the haemoglobin oxygen association curve. Considering the detail in this chapter, I was surprised and disappointed that there was no explanation on how reduced ventilation–perfusion ratios produced a low arterial P_{O_2}. The chapter on carbon dioxide transport in blood was again excellent, and though I found the chapter on acid–base balance over complicated there is a clear description of the difference between in vivo and in vitro acid–base measurements.

This introductory section is followed by a good chapter on the clinical approach to blood gas and acid–base problems. The authors rightly emphasize the importance of interpreting the results of these tests in terms of the patient's clinical history and examination. I was sorry that they had omitted a derivation of Bohr's equation and also had not derived the Shunt equation in this chapter, but they do quite rightly emphasize the importance of the alveolar–arterial oxygen tension gradient. In discussing the clinical applications of acid–base neasurements again the text is over-complicated. Many doctors now carry round their own preferred chart or diagram of in vivo acid–base changes and plot the results of their own patients on these. A section illustrating acid–base changes in disease and how these changed with treatment, plotted on an acid–base diagram, would have been very helpful The authors do, however, emphasize the importance of using an in vivo rather than in vitro method of interpreting acid–base data.

There is a very good chapter on quality control and a very useful one on blood gas correction factors.

The authors have resolutely set their face against kilopascals. This is a pity in 1980. At the very least blood gas tensions could have been written with the value in kilopascals, in brackets. Many hospitals now present their blood gas data in SI units and it is irritating for staff working in such hospitals to read a book in which kilopascals are not metioned. Their omission is more than irritating, however, since it leads to inconsistences where gas contents in blood are concerned. CO_2 content is described throughout in millimoles per litre, while oxygen content is most often described in millilitres per 100 millilitres, though millimoles do creep in, in brackets, at the bottom of p. 19!

This is a good book and it should hel to clear up many areas of ignorance and uncertainty for many hospital doctors who are increasingly using and relying on blood gas and acid–base measurements.

B. D. W. Harrison

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